```
? b 411
     02dec02 12:10:19 User217743 Session D581.2
        $0.00   0.071 DialUnits File410
    $0.00  Estimated cost File410
    $0.01  TELNET
    $0.01  Estimated cost this search
    $0.01  Estimated total session cost   0.238 DialUnits File
411:DIALINDEX(R)

DIALINDEX(R)
  (c) 2002 The Dialog Corporation plc

*** DIALINDEX search results display in an abbreviated *** *** format unless you enter the SET DETAIL ON command. *** ? set files biochem
>>>       162 is unauthorized
>>>1 of the specified files is not available
  You have 22 files in your file list.
  (To see banners, use SHOW FILES command)
? s fsh and expression

Your SELECT statement is:
  s fsh and expression

       Items   File
       -----   ----
        1772    5: Biosis Previews(R)_1969-2002/Nov W3
2759    34: SciSearch(R) Cited Ref Sci_1990-2002/Dec W1
 541    50: CAB Abstracts_1972-2002/Oct
          25    65: Inside Conferences_1993-2002/Dec W1
1060    71: ELSEVIER BIOBASE_1994-2002/Dec W1
        1406    73: EMBASE_1974-2002/Nov W4
          98    94: JICST-EPlus_1985-2002/Sep W5
          40    98: General Sci Abs/Full-Text_1984-2002/Oct
   10   103: Energy SciTec_1974-2002/Nov B2
           9   143: Biol. & Agric. Index_1983-2002/Oct
 646   144: Pascal_1973-2002/Dec W1
        1558   155: MEDLINE(R)_1966-2002/Nov W3
         168   156: ToxFile_1965-2002/Nov W3
          21   172: EMBASE Alert_2002/Dec W1
           5   370: Science_1996-1999/Jul W3
         487   399: CA SEARCH(R)_1967-2002/UD=13723
          35   434: SciSearch(R) Cited Ref Sci_1974-1989/Dec
  17 files have one or more items; file list includes 22 files.

? s fsh and (induced or induces or induction) and expression
Your SELECT statement is:
  s fsh and (induced or induces or induction) and expression
       Items   File
       -----   ----
         507    5: Biosis Previews(R)_1969-2002/Nov W3
1022    34: SciSearch(R) Cited Ref Sci_1990-2002/Dec W1
 148    50: CAB Abstracts_1972-2002/Oct
           1    65: Inside Conferences_1993-2002/Dec W1
 356    71: ELSEVIER BIOBASE_1994-2002/Dec W1
         496    73: EMBASE_1974-2002/Nov W4
          17    94: JICST-EPlus_1985-2002/Sep W5
          32    98: General Sci Abs/Full-Text_1984-2002/Oct
    2   103: Energy SciTec_1974-2002/Nov B2
           1   143: Biol. & Agric. Index_1983-2002/Oct          139
144: Pascal_1973-2002/Dec W1
         519   155: MEDLINE(R)_1966-2002/Nov W3
          83   156: ToxFile_1965-2002/Nov W3
           7   172: EMBASE Alert_2002/Dec W1
           4   370: Science_1996-1999/Jul W3
          62   399: CA SEARCH(R)_1967-2002/UD=13723
           5   434: SciSearch(R) Cited Ref Sci_1974-1989/Dec
  17 files have one or more items; file list includes 22 files.
? rf
Your last SELECT statement was:
  S FSH AND (INDUCED OR INDUCES OR INDUCTION) AND EXPRESSION
Ref      Items   File
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N1        1022    34: SciSearch(R) Cited Ref Sci_1990-2002/Dec W1 N2
          519   155: MEDLINE(R)_1966-2002/Nov W3
N3        507     5: Biosis Previews(R)_1969-2002/Nov W3 N4
  496    73: EMBASE_1974-2002/Nov W4
N5        356    71: ELSEVIER BIOBASE_1994-2002/Dec W1
N6        148    50: CAB Abstracts_1972-2002/Oct
N7        139   144: Pascal_1973-2002/Dec W1
N8         83   156: ToxFile_1965-2002/Nov W3
N9         62   399: CA SEARCH(R)_1967-2002/UD=13723
N10        32    98: General Sci Abs/Full-Text_1984-2002/Oct
17 files have one or more items; file list includes 22 files.
     - Enter P or PAGE for more -
? p
Your last SELECT statement was:
  S FSH AND (INDUCED OR INDUCES OR INDUCTION) AND EXPRESSION
Ref      Items   File
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N11        17    94: JICST-EPlus_1985-2002/Sep W5
N12         7   172: EMBASE Alert_2002/Dec W1
N13         5   434: SciSearch(R) Cited Ref Sci_1974-1989/Dec
N14         4   370: Science_1996-1999/Jul W3
N15         2   103: Energy SciTec_1974-2002/Nov B2
N16         1    65: Inside Conferences_1993-2002/Dec W1 N17
    1   143: Biol. & Agric. Index_1983-2002/Oct N18          0 . 6:
NTIS_1964-2002/Dec W1
N19         0    40: Enviroline(R)_1975-2002/Nov
N20         0    68: Env.Bib._1972-2002/Jun
  17 files have one or more items; file list includes 22 files.
     - Enter P or PAGE for more -
? pause
>>> PAUSE started.
? b 155
>>> PAUSE ended.
     02dec02 12:13:29 User217743 Session D581.3
        $0.00   0.000 DialUnits FilePause
    $0.00  Estimated cost FilePause
        $4.15   2.374 DialUnits File411
    $4.15  Estimated cost File411
    $0.86  TELNET
    $5.01  Estimated cost this search
    $5.02  Estimated total session cost   2.612 DialUnits
File 155:MEDLINE(R) 1966-2002/Nov W3
*File 155: For updating information please see Help News155.
Alert feature enhanced with customized scheduling. See HELP ALERT.
    Set  Items  Description
    ---  -----  -----------
? s fsh and (induced or induces or induction) and expression
19566  FSH
     1074092  INDUCED
       82725  INDUCES
      220765  INDUCTION
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530352 EXPRESSION
S1 519 FSH AND (INDUCED OR INDUCES OR INDUCTION) AND EXPRESSION ? s1 and fsh()induced
2857159 1
19566 FSH
1074092 INDUCED
465 FSH(W)INDUCED
S2 312 1 AND FSH()INDUCED
? s s1 and fsh()induced
519 S1
19566 FSH
1074092 INDUCED
465 FSH(W)INDUCED
S3 104 S1 AND FSH()INDUCED
? s s3 and py>2000
104 S3
954174 PY>2000
S4 25 S3 AND PY>2000
? s s3 not s4
104 S3
25 S4
S5 79 S3 NOT S4
? t s5/3,ab/all

5/3,AB/1
DIALOG(R)File 155:MEDLINE(R)

11193718 21222626 PMID: 11324510
Prolactin inhibition of *FSH*-*induced* tissue type plasminogen activator *expression* in cultured rat granulosa cells. Liu Y X; Liu H Z; Chen Y J; Tor N Y
State Key Laboratory of Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100080. Liuyx@panda.ioz.ac.cn Sheng li xue bao Acta physiologica Sinica (China) Feb 1998, 50 (1) p11-8, ISSN 0371-0874 Journal Code: 20730130R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
This study was designed to investigate whether prolactin (PRL) affects coordinated regulation of tissue plasminogen activator (tPA) and plasminogen activator inhibitor type-I(PAI-I) gene *expression* in rat granulosa cells in vitro. Several methods, such as SDS-PAGE, immunoblot etc. were used to detect the effect of PRL on tPA and PAI-I gene *expression* . The results demonstrated: (1) PRL increases PAI-I mRNA production in cultured granulosa cells. Inclusion of follicle stimulating hormone (*FSH*) with PRL has a synergistic effect on the increase of PAI-I mRNA levels. After 48 h culture in the presence of *FSH* with PRL, a 7.8-fold increase in PAI-I mRNA levels is observed as compared with PRL alone. The synergistic increase in PAI-I mRNA levels occurs in a dose- and time-dependent manner; (2) the increase in PAI-I mRNA synthesis in the cells by PRL alone, or PRL in combination with *FSH* , is well correlated with the changes of PAI-I activity levels in the conditioned media; (3) PRL in culture also decreases *FSH*-*induced* tPA activity level in a dose-dependent fashion. The decrease in *FSH*- *induced* tPA activity level by PRL is correlated with an increase in the amount of PA-PAI-I complexes in the conditioned media. This suggests that the decline of tPA activity is related to neutralization of tPA by the increased PAI-I activity in the media.

102(b)

5/3,AB/2
DIALOG(R)File 155:MEDLINE(R)

10990018 20564326 PMID: 10998422
Bone morphogenetic protein-15. Identification of target cells and biological functions.
Otsuka F; Yao Z; Lee T; Yamamoto S; Erickson G F; Shimasaki S
Department of Reproductive Medicine, University of California, San Diego, School of Medicine, La Jolla, California 92093-0633, USA.
Journal of biological chemistry (UNITED STATES) Dec 15 2000, 275 (50) p39523-8, ISSN 0021-9258 Journal Code: 2985121R
late
Contract/Grant No.: U54HD12303; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In developing ovarian follicles, the regulation of cell proliferation and differentiation is tightly coordinated. Precisely how this coordination is achieved is unknown, but recent observations have suggested that molecules emitted by the oocyte are involved in the process. The newly discovered oocyte-specific growth factor, bone morphogenetic protein-15 (BMP-15), is one such molecule. At present, nothing is known about the target cells and biological functions of BMP-15. To fill this gap in our knowledge, recombinant BMP-15 and its antibody were produced and used to determine BMP-15 *expression* and bioactivity. BMP-15 mRNA and protein were shown to be co-expressed in oocytes throughout folliculogenesis, supporting the idea that BMP-15 is a physiological regulator of follicle cell proliferation and/or differentiation. To test this, we used primary cultures of rat granulosa cells (GCs). We found that BMP-15 is a potent stimulator of GC proliferation, and importantly, the mitogenic effect was follicle-stimulating hormone (*FSH*)-independent. By contrast, BMP-15 alone had no effect on steroidogenesis. However, it produced a marked decrease in *FSH*-*induced* progesterone production, but had no effect on *FSH*-stimulated estradiol production. This result indicates that BMP-15 is a selective modulator of *FSH* action. In summary, this study identifies GCs as the first target cells for BMP-15. Moreover, it identifies the stimulation of GC proliferation and the differential regulation of two crucial steroid hormones as the first biological functions of BMP-15. Significantly, BMP-15 is the first growth factor that can coordinate GC proliferation and differentiation in a way that reflects normal physiology.

5/3,AB/3
DIALOG(R)File 155:MEDLINE(R)

10948521 20477577 PMID: 11026553
Demonstration of 2,3,7,8-tetrachlorodibenzo-p-dioxin attenuation of P450 steroidogenic enzyme mRNAs in rat granulosa cell in vitro by competitive reverse transcriptase-polymerase chain reaction assay.
Dasmahapatra A K; Wimpee B A; Trewin A L; Wimpee C F; Ghorai J K; Hutz R J
Department of Biological Sciences, University of Wisconsin-Milwaukee, 53211, USA.
Molecular and cellular endocrinology (IRELAND) Jun 2000, 164 (1-2) p5-18, ISSN 0303-7207 Journal Code: 7500844
Contract/Grant No.: ES04184; ES; NIEHS; ES08342; ES;

NIEHS Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We investigated the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), in prepubertal (PP) and adult (A) rat granulosa cells (GC) in vitro by examining the changes in estrogen secretion, aromatase enzyme activity and mRNAs for steroidogenic enzymes P450scc, 3beta-HSDI, P450arom; and for components of the AHR signaling pathway-CYP1A1, aromatic hydrocarbon receptor (AHR), and the AHR nuclear translocator protein (ARNT). In PP and A rat GC, TCDD (3.1 nM) reduced estrogen secretion at 48 h without altering aromatase enzyme activity. Addition of *FSH* (50 ng/ml) increased aromatase activity in GC with or without TCDD. *FSH*-*induced* aromatase activity was significantly reduced by TCDD (3.1 nM) at 48 h. Semi-quantitative RT-PCR showed a significant increase in CYP1A1 mRNA both at 24 and 48 h with TCAP, while a significant reduction in P450scc and P450arom mRNA was observed with competitive RT-PCR. All steroidogenic enzyme mRNAs were significantly lower in adults than in PP GC. We conclude that in rat GC, TCDD modulates the level of cytochrome P450 enzymes involved in the steroid biosynthetic cascade. This effect may be attributable to AHR interaction with dioxin-responsive elements present in the genes encoding these enzymes.

5/3,AB/4
DIALOG(R)File 155:MEDLINE(R)

10882335 20427132 PMID: 10975420
Characterization of a novel transcript of 14-3-3 theta in Sertoli cells. Chaudhary J; Skinner M K
Center for Reproductive Biology, School of Molecular Biosciences, Washington State University, Pullman 99164-4231, USA.
Journal of andrology (UNITED STATES) Sep-Oct 2000, 21 (5) p730-8, ISSN 0196-3635 Journal Code: 8106453
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The isoforms of the highly conserved and ubiquitously expressed 14-3-3 family of proteins function primarily as adapters that modulate interactions between components of various cellular signaling and cell cycle regulatory pathways. Low levels of 14-3-3 isoforms appear to be expressed in most tissues, but specific isoforms or combinations have been shown to be overexpressed in a cell-specific manner. In the present study we show that the theta isoform of 14-3-3 is expressed in Sertoli cells. Although previous reports have shown the presence of a 14-3-3 theta isoform in mouse testicular germ cells, this report demonstrates the presence of the 14-3-3 theta isoform in rat Sertoli cells. The 14-3-3 theta isoform isolated from rat Sertoli cells appears to have a truncated 3' UTR, which makes the transcript shorter by 244 bp, compared with its brain counterpart. Northern blot analysis suggests that the 14-3-3 theta isoform may also be present in other testicular cell types and tissues. The truncation of the 3' UTR suggests a potential role in regulating cell-specific *expression* of 14-3-3 theta. The *expression* of 14-3-3 theta in Sertoli cells was confirmed by Northern blot, polymerase chain reaction, Western blot, and immunocytochemical analysis. The levels of 14-3-3 theta mRNA and protein in Sertoli cells remained unchanged in response to the gonadotropin, *FSH*. Consistent with the absence of the effect of *FSH* on the *expression* of 14-3-3 theta, an antisense oligonucleotide to 14-3-3 theta had no effect on *FSH*-*induced* activation of the transferrin promoter in Sertoli cells. The widespread *expression* of 14-3-3 theta in testis and the lack of effect of *FSH* on levels of its *expression* suggest that 14-3-3 theta influences Sertoli cell function in an *FSH*-independent manner.

5/3,AB/5
DIALOG(R)File 155:MEDLINE(R)

10871737 20428664 PMID: 10869352
Activation of extracellular-regulated kinase pathways in ovarian granulosa cells by the novel growth factor type 1 follicle-stimulating hormone receptor. Role in hormone signaling and cell proliferation. Babu P S; Krishnamurthy H; Chedrese P J; Sairam M R
Molecular Reproduction Research Laboratory, Clinical Research Institute of Montreal, Montreal, Quebec H2W 1R7, Canada.
Journal of biological chemistry (UNITED STATES) Sep 8 2000, 275 (36) p27615-26, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Follicle-stimulating hormone (*FSH*) regulated growth and function of the ovarian follicle was previously thought to be mediated solely through activation of G(s)-coupled receptors. In this study, we show for the first time that this function is predominantly mediated through the alternatively spliced and novel growth factor type 1 receptor (oFSH-R3) that is also present in the ovary. Immortalized granulosa cells lacking endogenous *FSH* receptors, when transfected with either oFSH-R3 cDNA (JC-R3) or the G(s)-coupled oFSH-R1 (JC-R1), expressed the corresponding glycosylated receptor. In JC-R3 or JC-R1 cells labeled with bromodeoxyuridine or [(3)H]thymidine, *FSH* stimulated the cells to progress through S-phase and divide. The growth promoting effect of recombinant *FSH* in JC-R3 cells was preceded by the rapid activation of ERK1 and ERK2. This effect was hormone-specific and transient. In JC-R3 cells inhibitors like calphostin C, PD98059, Ag 18, or calcium chelators EGTA or 1,2-bis(O-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid/AM inhibited both mitogen-activated protein kinase activation and bromodeoxyuridine incorporation. *FSH* *induced* phosphorylation of the *FSH*-R3 receptor was blocked by pretreating cells with calphostin C. There was no cAMP *induction* by *FSH* in JC-R3 cells. The cAMP independent growth promoting effect of *FSH* is mediated by activation of Ca(2+) and mitogen-activated protein kinase-dependent pathways. Thus, alternative splicing of a G-protein coupled receptor creates the *expression* of a novel receptor motif that can mediate a widely recognized function of the glycoprotein hormone.

5/3,AB/6
DIALOG(R)File 155:MEDLINE(R)

10839566 20408123 PMID: 10954035
Expression of steroidogenic acute regulatory protein (StAR) in rat granulosa cells.

Minegishi T; Tsuchiya M; Hirakawa T; Abe K; Inoue K; Mizutani T; Miyamoto K

Department of Obstetrics and Gynecology, School of Medicine, Gunma University, Maebashi, Japan. tminegis@sb.gunma-u.ac.jp

Life sciences (ENGLAND) 2000, 67 (9) p1015-24, ISSN 0024-3205 Journal Code: 0375521

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Steroidogenic acute regulatory protein (StAR) is a vital mitochondrial protein that is indispensable for the synthesis of steroids. To study the mechanisms of regulation of StAR in rat granulosa cells, we used granulosa cells obtained from diethylstilbestrol-treated immature rats. Northern blot analysis revealed two major transcripts of about 3.6 kb and 1.6 kb of rat StAR mRNA. Rat StAR mRNA had strongly increased within 2 h due to the treatment of *FSH* or 8-Br-cAMP in this culture, a parallel increase of transcripts of both sizes was observed. Compared to the control, StAR mRNA levels increased in a dose-dependent manner in the presence of increasing concentrations of *FSH* (1-100 ng/ ml) and 8-Br-cAMP (0.25-5 mM). Although co-treatment of rat granulosa cells with *FSH* and TGF-beta did not change *FSH*-*induced* StAR mRNA levels, these levels in granulosa cells were markedly increased by pretreatment with TGF-beta before being acutely (2 h) stimulated with an effective dose of *FSH*. The stimulatory effect of TGF-beta was time- and concentration-dependent (1-30 ng/ml).

5/3,AB/7
DIALOG(R)File 155:MEDLINE(R)

10819849 20374680 PMID: 10915218

Inhibitory effect of retinoic acid on the development of immature porcine granulosa cells to mature cells.

Hattori M; Takesue K; Nishida N; Kato Y; Fujihara N

Laboratory of Reproductive Physiology, Graduate School of Bioresource and Bioenvironmental Sciences, Kyushu University, Hakozaki, Fukuoka 812-8581, Japan. mhattori@agr.kyushu-u.ac.jp

Journal of molecular endocrinology (ENGLAND) Aug 2000, 25 (1) p53-61 , ISSN 0952-5041 Journal Code: 8902617

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The present study investigated the effect of retinoic acid (RA) on the differentiation of granulosa cells prepared from porcine ovaries. The granulosa cells were precultured for 15 h, then cultured for 48 h with *FSH* and further treated for 24 h with LH in order to induce their transformation into luteal cells. After the cells had been exposed to 1 microM retinoids (RA, retinal and retinol) for 87 h, analysis of the LH receptor mRNA *expression* , an indicator of granulosa cell differentiation, was carried out by using semiquantitative RT-PCR. The results showed that there was a decrease in LH receptor mRNA levels, and that RA had a more potent effect on these levels than the other two retinoids. When cells were exposed to RA in the immature stage (before the addition of *FSH*) or the early stage of development (0-24 h after the addition of *FSH*), *expression* of LH receptor mRNA was greatly diminished. When the immature cells were cultured for 15 h with RA, then washed and cultured for 48 h with *FSH* and for 24 h with LH, the *expression* of LH receptor mRNA was not reversed. In the differentiated cells (24 h after the addition of *FSH*), however, RA no longer had any inhibitory effect. When the immature cells were exposed to RA, *FSH*-*induced* *expression* of c-fos mRNA was markedly decreased. In contrast, *expression* of c-jun and activating transcription factor-4 mRNAs remained constant. However, the *expression* of c-fos mRNA was not decreased by forskolin. The results indicate that RA is a potent inhibitor in the immature stage of porcine granulosa cell differentiation, probably through decreased *expression* of *FSH* receptor, but that RA does not inhibit differentiation in the mature stage of the cells.

5/3,AB/8
DIALOG(R)File 155:MEDLINE(R)

10809611 20373869 PMID: 10919260

Role of winged helix transcription factor (WIN) in the regulation of Sertoli cell differentiated functions: WIN acts as an early event gene for follicle-stimulating hormone.

Chaudhary J; Mosher R; Kim G; Skinner M K

Center for Reproductive Biology, Washington State University School of Molecular Biosciences, Pullman 99164-4231, USA.

Endocrinology (UNITED STATES) Aug 2000, 141 (8) p2758-66, ISSN 0013-7227 Journal Code: 0375040

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Members of the winged helix transcription factor family are known to regulate epithelial cell differentiation by regulating cell-specific gene *expression* . rWIN is a newly discovered member of the winged helix family shown to be present in the adult rat testis. In the testis the human homolog of rWIN, HFH-11, was localized to the germ cells (i.e. spermatocytes and spermatids) undergoing spermatogenesis. In the present study we show that rWIN is also expressed in testicular Sertoli cells. Sertoli cells are the epithelial component of the seminiferous tubule and provide both the cytoarchitectural support and the microenvironment for developing germ cells. The presence of rWIN in Sertoli cells was confirmed by Northern blot and RT-PCR analysis. The rWIN transcript size in the Sertoli cells was different from the germ cell transcript that is probably due to alternative splicing or modifications of the 3'-untranslated region. At least two spliced variants of rWIN were observed in the Sertoli cells corresponding to the deletion of an exon in the DNA-binding region. Long term stimulation of cultured Sertoli cells with the gonadotropin *FSH* down-regulated rWIN *expression*. In contrast, short-term stimulation (2 h) transiently up-regulated rWIN *expression*. The *FSH*- *induced* transient stimulation of rWIN precedes *expression* of the transferrin gene that is a marker of Sertoli cell differentiation. *FSH*-*induced* transferrin promoter activity was inhibited when cultured Sertoli cells were treated with an antisense oligonucleotide to rWIN. Interestingly, the constitutive overexpression of the DNA-binding domain of rWIN also down-regulated transferrin promoter activity. Analysis of the transferrin promoter with various deletion mutations suggested that rWIN acts at an upstream gene of the transferrin promoter. The results indicate that a transient up-regulation of rWIN in part mediates the ability of *FSH*

to activate the transferrin promoter, which can be inhibited with a rWIN antisense oligonucleotide or constitutive *expression* of the rWIN DNA-binding domain. The current study demonstrates that rWIN acts as an early event gene for *FSH* actions on Sertoli cells and that rWIN appears to have a role in the regulation of Sertoli cell differentiated functions.

5/3,AB/9
DIALOG(R)File 155:MEDLINE(R)

10775826 20331465 PMID: 10875237
Calcium ions positively modulate follicle-stimulating hormone- and exogenous cyclic 3',5'-adenosine monophosphate-driven transcription of the P450(scc) gene in porcine granulosa cells.
Jayes F C; Day R N; Garmey J C; Urban R J; Zhang G; Veldhuis J D Department of Internal Medicine, NIH Specialized Cooperative Center in Reproduction Research, University of Virginia Health Sciences Center, Charlottesville 22908, USA.
Endocrinology (UNITED STATES) Jul 2000, 141 (7) p2377-84, ISSN 0013-7227 Journal Code: 0375040
Contract/Grant No.: 1-F32-HD-08284-01; HD; NICHD; HD-16393; HD; NICHD; T32-DK-07646; DK; NIDDK; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Given the evident modulation of *FSH*-*induced* steroidogenesis by Ca2+ in granulosa cells, we here test the hypothesis that Ca2+ controls *expression* of the enzymatically rate-limiting cytochrome P450(scc) (CYP11A) gene. To test this postulate, we quantitated the ability of Ca2+ to regulate: 1) transcriptional activity of a transiently transfected luciferase reporter gene driven by a 2.32-kb 5'-upstream fragment of the porcine P450(scc) gene promoter region; and 2) accumulation of endogenous P450(scc) transcripts in primary monolayer cultures of porcine granulosa cells. To this end, granulosa cells were stimulated for 4 h with *FSH* (15 ng/ml, NIDDK-oFSH-20) or 8-Bromo-cAMP (8 Br-cAMP, 1 mM) in serum-free medium containing either 1.8 mM Ca2- or no added Ca2+ with 100 microM EGTA or 100 microM CoCl2. In the presence of extracellular Ca2+, *FSH* and 8 Br-cAMP stimulated *expression* of the transfected P450(scc) promoter-reporter fusion construct by 5.6 +/- 1.1 and 3.6 +/- 0.67-fold, respectively over Ca2+-containing unstimulated control (P < or = 0.04, n = 5-6 experiments). The foregoing two agonists augmented 4-h progesterone production by cultured granulosa cells by 1.8 +/- 0.11 and 1.6 +/- 0.16-fold, respectively (P < or = 0.001 for *FSH* and P < or = 0.01 for 8 Br-cAMP). *FSH* and 8 Br-cAMP also significantly elevated endogenous P450(scc) transcript levels as measured by homologous solution-hybridization RNase protection assay; i.e. by 3.1 +/- 0.49 and 2.9 +/- 0.45-fold, respectively (P < or = 0.001). In Ca2+-free/EGTA-supplemented medium, basal luciferase reporter-gene activity and endogenous P450(scc) messenger RNA accumulation in granulosa cells declined to 34 +/- 12% and 78 +/- 12%, respectively, of corresponding values in control (unstimulated Ca2+-containing) cultures. Extracellular Ca2+ deprivation inhibited the stimulatory effect of *FSH* (and 8 Br-cAMP) on P450(scc) promoter-luciferase reporter *expression* to 58 +/- 30% (and 58 +/- 23%), and restrained endogenous P450(scc) message accumulation to 86 +/- 15% (and 96 +/- 18%) of the value in Ca2+-containing control. Extracellular Ca2+ withdrawal suppressed *FSH* (and 8 Br-cAMP)-driven progesterone production over 4 h to basal levels but did not alter *FSH* -stimulated cAMP accumulation by granulosa cells. Ca2+-deprived cells exposed to serum-containing media regained P450(scc) responsiveness to both agonists. Antagonism of cellular uptake of Ca2+ and other divalent cations via administration of cobalt chloride (100 microM) inhibited *FSH* and 8 Br-cAMP's stimulation of endogenous (but not exogenous promoter-driven) P450(scc) gene *expression*. In contrast, granulosa-cell concentrations of messenger RNA's encoding sterol-carrier protein-2 (SCP-2) and the low density lipoprotein receptor were not altered by Ca2+ withdrawal. In summary, uptake of extracellular Ca2+ by porcine granulosa cells significantly potentiates transactivation of the endogenously expressed and exogenously transfected P450(scc) gene by *FSH* and 8 Br-cAMP. The agonistic impact of Ca2+ on P450(scc) promoter activity is requisite downstream of *FSH*-*induced* cAMP second-messenger signaling.

5/3,AB/10
DIALOG(R)File 155:MEDLINE(R)

10655399 20208441 PMID: 10746652
Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin on the *expression* of follicle-stimulating hormone receptors during cell differentiation in cultured granulosa cells.
Hirakawa T; Minegishi T; Abe K; Kishi H; Inoue K; Ibuki Y; Miyamoto K Department of Obstetrics and Gynecology, School of Medicine, Gunma University, Maebashi, Japan. tminegis@sb.gunma-u.ac.jp
Endocrinology (UNITED STATES) Apr 2000, 141 (4) p1470-6, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin; TCDD) is a common environmental pollutant causing public concern. Using a cell culture system derived from rat granulosa cells that provides unique advantages for studying the molecular mechanisms underlying the action of TCDD, the influences of TCDD on *FSH* receptor (*FSH*-R) *induction* were examined. The treatment with *FSH* produced, as expected, a substantial increase in specific *FSH*-R *expression* , whereas concurrent treatment with the environmental amount of TCDD (10 pM) resulted in a significant decrease in *FSH* -R after being cultured from 24-72 h. Cotreatment with *FSH* (30 ng/ml) and increasing doses of TCDD inhibited the levels of *FSH*-*induced* *FSH*-R messenger RNA (mRNA) in a dose-dependent manner. Treatment with 8-Br-cAMP (1 mM) produced a significant increase in *FSH*-R mRNA; concurrent treatment with TCDD (10 pM) produced a significant attenuation of 8-Br-cAMP action. These findings suggest that the ability of TCDD to interfere with *FSH* action, as regards the *induction* of *FSH*-Rs, is exerted at sites distal to those involved in cAMP generation. Because a single transcript of 5.2 kb was seen for the Ah receptor in this granulosa cell system, the effects of TCDD may be mediated by this specific receptor. The rates of *FSH* -R mRNA gene transcription, assessed by nuclear run-on transcription assay, were decreased by the addition of TCDD. The effect of TCDD on *FSH*-R mRNA stability was determined by measuring the decay of *FSH*-R mRNA under conditions known to inhibit transcription. The decay curve for the 2.4-kb *FSH* -R mRNA transcript was not significantly changed after the addition of TCDD. These

findings showed that the effect of TCDD on *FSH*-R mRNA was, at least in part, the result of decreased transcription.

5/3,AB/11
DIALOG(R)File 155:MEDLINE(R)

10649353 20164076 PMID: 10699459
The mechanisms of retinoic acid-*induced* regulation on the follicle-stimulating hormone receptor in rat granulosa cells.
Minegishi T; Hirakawa T; Kishi H; Abe K; Tano M; Abe Y; Miyamoto K Department of Obstetrics and Gynecology, School of Medicine, Gunma University, Maebashi, Gunma, Japan. tminegis@sb.gunma-u.ac.jp Biochimica et biophysica acta (NETHERLANDS) Feb 28 2000, 1495 (3) p203-11, ISSN 0006-3002 Journal Code: 0217513
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The present study was undertaken to identify the mechanisms underlying the effect of retinoic acid (RA) on follicle-stimulating hormone receptor (*FSH*-R) in rat granulosa cells. Treatment with *FSH* produced a substantial increase in *FSH* -R mRNA level, as was expected, while concurrent treatment with increasing concentrations of RA brought about dose-dependent decreases in *FSH*-*induced* *FSH*-R mRNA, with a maximal inhibition one-third lower than that *induced* by *FSH* alone. RA, either alone or in combination with *FSH*, did not affect intracellular cAMP levels, while it inhibited the effect of 8-Br-cAMP on *FSH*-R mRNA production. These results suggested that RA diminished the action of *FSH* on *FSH*-R *expression* at sites distal to cAMP generation in the granulosa cells. Whether the effect of RA and *FSH* on *FSH* -R mRNA levels was the result of decreased transcription and/or altered mRNA stability was also investigated. The rate of *FSH* receptor mRNA gene transcription, assessed by nuclear run-on transcription assay, was found to decrease by the addition of RA. On the other hand, the decay curves for the 2.4 kb *FSH* -R mRNA transcript in primary granulosa cells did not alter the slope of the *FSH*-R mRNA decay curve in the presence of RA. Our data suggests for the first time that the effect of RA on *FSH*-R *expression* is possibly mediated by the reduction of the *FSH*-R mRNA level due to a negative regulation of the *FSH* -R gene in the presence of *FSH*. These findings assist in understanding the molecular mechanism underlying the effect of RA on reproductive function in rat granulosa cells.

5/3,AB/12
DIALOG(R)File 155:MEDLINE(R)

10640268 20166960 PMID: 10700395
Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin on the *expression* of luteinizing hormone receptors during cell differentiation in cultured granulosa cells.
Hirakawa T; Minegishi T; Abe K; Kishi H; Ibuki Y; Miyamoto K Department of Obstetrics, Gynecology School of Medicine, Gunma University, Maebashi, Gunma, 371-8511, Japan.
Archives of biochemistry and biophysics (UNITED STATES) Mar 15 2000, 375 (2) p371-6, ISSN 0003-9861 Journal Code: 0372430
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD) is a common environmental pollutant causing public concern. By use of a cell culture system derived from rat granulosa cells that provides unique advantages for studying the molecular mechanisms underlying the action of TCDD, the influence of TCDD on luteinizing hormone receptor (LHR) *induction* was examined. Treatment with follicle-stimulating hormone (*FSH*) produced, as expected, a substantial increase in specific LHR *expression*; concurrent treatment with TCDD (10 pM) resulted in a significant decrease in LHR after 24 h. Cotreatment with 30 ng/ml *FSH* and increasing doses of TCDD inhibited the levels of *FSH*-*induced* LHR mRNA in a dose-dependent manner, and 1 pM TCDD inhibited *FSH*-*induced* LHR significantly after 48 h. The rate of LHR mRNA gene transcription, assessed by nuclear run-on transcription assay, was found to decrease after addition of TCDD. The decay curves for the 5.4-kb LHR mRNA transcript showed a significant decrease after addition of TCDD. Copyright 2000 Academic Press.

5/3,AB/13
DIALOG(R)File 155:MEDLINE(R)

10580661 20111078 PMID: 10642569
A role of insulin-like growth factor I for follicle-stimulating hormone receptor *expression* in rat granulosa cells.
Minegishi T; Hirakawa T; Kishi H; Abe K; Abe Y; Mizutani T; Miyamoto K Department of Obstetrics and Gynecology, School of Medicine, Gunma University, Maebashi, Gunma 371-8511, Japan. tminegis@sb.gunma-u.ac.jp Biology of reproduction (UNITED STATES) Feb 2000, 62 (2) p325-33, ISSN 0006-3363 Journal Code: 0207224
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The present study was undertaken to identify the mechanisms underlying the effect of insulin-like growth factor I (IGF-I) on *FSH* receptor (FSHR) in rat granulosa cells. Treatment with *FSH* produced a substantial increase in FSHR mRNA level, as was expected, while concurrent treatment with increasing concentrations of IGF-I brought about dose-dependent increases in *FSH*-*induced* FSHR mRNA, with a maximal response 2.8-fold greater than that *induced* by *FSH* alone. IGF-I, either alone or in combination with *FSH*, did not affect intracellular cAMP levels, whereas it enhanced the effect of 8-bromo (Br)-cAMP on FSHR mRNA production. Taken together, these findings suggest that the ability of IGF-I to enhance *FSH* action concerning the *induction* of FSHR is exerted at sites distal to cAMP generation. We then investigated whether the effect of IGF-I and *FSH* on FSHR mRNA levels was the result of increased transcription and/or altered mRNA stability. The rates of FSHR mRNA gene transcription, assessed by nuclear run-on transcription assay, were not increased by the addition of IGF-I. On the other hand, the decay curves for the 2. 4-kilobase (kb) FSHR mRNA transcript in primary granulosa cells significantly altered the slope of the FSHR mRNA decay curve in the presence of IGF-I and increased the half-life of the FSHR mRNA transcript. These data suggest a possible role for changes in FSHR mRNA stability in the IGF-I-*induced* regulation of FSHR in rat granulosa cells. Treatment with activin produced a substantial increase in FSHR mRNA level, as was expected, and concurrent treatment with

IGF-I did not affect activin-*induced* FSHR mRNA. Our data suggest that the IGF-I effect on FSHR *expression* is related to cAMP production *induced* by *FSH* and may maintain FSHR mRNA level because of prolonged FSHR mRNA stability.

5/3,AB/14
DIALOG(R)File 155:MEDLINE(R)

10554568 20088611 PMID: 10620339
Retinoic acid (RA) represses follicle stimulating hormone (*FSH*)- *induced* luteinizing hormone (LH) receptor in rat granulosa cells. Minegishi T; Hirakawa T; Kishi H; Abe K; Ibuki Y; Miyamoto K Department of Obstetrics and Gynecology, School of Medicine, Gunma University, Maebashi, Gunma, 371-8511, Japan. tminegis@sb.gunma-u.ac.jp Archives of biochemistry and biophysics (UNITED STATES) Jan 1 2000, 373 (1) p203-10, ISSN 0003-9861 Journal Code: 0372430
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The present study was undertaken to identify the mechanisms underlying the effect of retinoic acid (RA) on the luteinizing hormone receptor (LH-R) in rat granulosa cells. Treatment with *FSH* produced a substantial increase in LH-R mRNA level, as was expected, while concurrent treatment with increasing concentrations of RA brought about dose-dependent decreases in *FSH*-*induced* LH-R mRNA. RA, either alone or in combination with *FSH* , did not affect intracellular cAMP levels, while it inhibited the effect of 8-Br-cAMP on LH-R mRNA production. Whether the effect of RA and *FSH* on LH-R mRNA levels was the result of decreased transcription and/or altered mRNA stability was also investigated. The rate of LH receptor mRNA gene transcription, assessed by nuclear run-on transcription assay, was inhibited by the addition of RA. The effect of RA on LH-R mRNA stability was determined by measuring the decay of LH receptor mRNA under conditions known to inhibit transcription. The decay curves for the 5.4-kb LH-R mRNA transcript showed a significant decrease after the addition of RA. It may be possible that RA not only inhibits *FSH*-*induced* transcription but also stimulates the production of destabilizing factors for the LH-R mRNA. These findings assist in understanding the molecular mechanism underlying the effect of RA on reproductive function in rat granulosa cells. Copyright 2000 Academic Press.

5/3,AB/15
DIALOG(R)File 155:MEDLINE(R)

10475093 20005512 PMID: 10537120
A role of insulin-like growth factor I in luteinizing hormone receptor *expression* in granulosa cells.
Hirakawa T; Minegishi T; Abe K; Kishi H; Ibuki Y; Miyamoto K Department of Obstetrics and Gynecology, School of Medicine, Gunma University, Maebashi, Japan.
Endocrinology (UNITED STATES) Nov 1999, 140 (11) p4965-71, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The present study was undertaken to identify the mechanisms underlying the effect of insulin-like growth factor (IGF-I) on LH receptor in rat granulosa cells. Treatment with *FSH* , as expected, produced a substantial increase in LH receptor messenger RNA (mRNA) level, and concurrent treatment with increasing concentrations of IGF-I brought about dose-dependent increases in *FSH*-*induced* LH receptor mRNA, with a maximal response 2.5-fold greater than that *induced* by *FSH* alone. IGF-I, either alone or in combination with *FSH*, did not affect intracellular cAMP levels, whereas it enhanced the effect of 8-bromo-cAMP on LH receptor mRNA production. We then investigated whether the effects of IGF-I and *FSH* on LH receptor mRNA levels are the results of increased transcription and/or altered mRNA stability. To determine whether the LH receptor 5'-flanking region plays a role in directing LH receptor mRNA *expression*, the proximal area of the LH receptor 5'-flanking regions were inserted into a transient *expression* vector, pGL-Basic, which contains luciferase as the reporter gene, and the resulting plasmids were transiently transfected into rat granulosa cells. Our studies show that the *FSH*-*induced* luciferase activity varied dependent upon the length of the 5'-flanking region sequence in the reporter gene. In addition, *FSH* (30 ng/ml) significantly enhanced the activity of 1379 bp of the LH receptor 5'-flanking region, but treatment with 10 ng/ml IGF-I alone did not significantly influence the activity of the LH receptor promoter or affect the increased promoter activity *induced* by *FSH*. The rates of LH receptor mRNA gene transcription, assessed by nuclear run-on transcription assay, were not increased by the addition of IGF-I. On the other hand, the decay curves for LH receptor mRNA transcript in primary granulosa cells showed a significant increase in the half-life after the addition of IGF-I. These data suggest a possible role for changes in LH receptor mRNA stability in the IGF-I-*induced* regulation of LH receptor in rat granulosa cells. This interface between circulating hormones and paracrine/autocrine systems could provide an important mechanism to amplify the effects of gonadotropic hormones at the local level.

5/3,AB/16
DIALOG(R)File 155:MEDLINE(R)

10413358 99405963 PMID: 10478849
Involvement of G protein-coupled receptor kinases and arrestins in desensitization to follicle-stimulating hormone action.
Troispoux C; Guillou F; Elalouf J M; Firsov D; Iacovelli L; De Blasi A; Combarnous Y; Reiter E
INRA/CNRS URA 1291, Station de Physiologie de la Reproduction des Mammiferes Domestiques, Nouzilly, France.
Molecular endocrinology (Baltimore, Md.) (UNITED STATES) Sep 1999, 13 (9) p1599-614, ISSN 0888-8809 Journal Code: 8801431
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
FSH rapidly desensitizes the *FSH*-receptor (*FSH*-R) upon binding. Very little information is available concerning the regulatory proteins involved in this process. In the present study, we investigated whether G protein-coupled receptor kinases (GRKs) and arrestins have a role in *FSH* -R desensitization, using a mouse Ltk 7/12 cell line stably overexpressing the rat *FSH*-R as a model. We found that

these cells, which express GRK2, GRK3, GRK5, and GRK6 as well as beta-arrestins 1 and 2 as detected by RT-PCR and by Western blotting, were rapidly desensitized in the presence of *FSH*. Overexpression of GRKs and/or beta-arrestins in Ltk 7/12 cells allowed us to demonstrate 1) that GRK2, -3, -5, -6a, and -6b inhibit the *FSH* -R-mediated signaling (from 71% to 96% of maximal inhibition depending on the kinase, P < 0.001); 2) that beta-arrestins 1 or 2 also decrease the *FSH* action when overexpressed (80% of maximal inhibition, P < 0.01) whereas dominant negative beta-arrestin 2 [319-418] potentiates it 8-fold (P < 0.001); 3) that beta-arrestins and GRKs (except GRK6a) exert additive inhibition on *FSH*-*induced* response; and 4) that *FSH*-R desensitization depends upon the endogenous *expression* of GRKs, since there is potentiation of the *FSH* response (2- to 3-fold, P < 0.05) with antisenses cDNAs for GRK2, -5, and -6, but not GRK3. Our results show that the desensitization of the *FSH*-*induced* response involves the GRK/arrestin system.

5/3,AB/17
DIALOG(R)File 155:MEDLINE(R)

10380170 99374572 PMID: 10446906
Functional and subcellular changes in the A-kinase-signaling pathway: relation to aromatase and Sgk *expression* during the transition of granulosa cells to luteal cells.
Gonzalez-Robayna I J; Alliston T N; Buse P; Firestone G L; Richards J S Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77030, USA.
Molecular endocrinology (Baltimore, Md.) (UNITED STATES) Aug 1999, 13 (8) p1318-37, ISSN 0888-8809 Journal Code: 8801431
Contract/Grant No.: CA-71514; CA; NCI; HD-16272; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The responsiveness of granulosa cells to *FSH* (cAMP) changes as these cells switch from the proliferative stage in growing follicles to the terminally differentiated, nonproliferating stage after LH-*induced* luteinization. To analyze this transition, two well characterized culture systems were used. 1) Granulosa cells isolated from immature rats were cultured in serum-free medium, a system that permits analysis of dynamic, short-term responses to hormones/cAMP. 2) Granulosa cells from preovulatory (PO) follicles that have been exposed in vivo to surge concentrations of hCG (PO/ hCG) were cultured in medium containing 1% FBS, a system that permits analyses of cells that have undergo irreversible, long-term changes associated with luteinization. To analyze the biochemical basis for the switch in cAMP responsiveness, the localization of A-kinase pathway components was related to the *expression* of two cAMP target genes, aromatase (CYP19) and serum-and glucocorticoid-*induced* kinase (Sgk). Components of the A-kinase pathway were analyzed by Western blotting and indirect immunofluorescence using specific antibodies to the C subunit, RIIalpha/beta subunits, CREB (cAMP-regulatory element binding protein), phospho-CREB, CBP (CREB binding protein), and Sgk. Cellular levels of C subunit and CREB were similar in all cell types and hormone treatments. CREB and CBP were nuclear; RIIalpha/beta was restricted to a cytoplasmic basket-like structure. Addition of *FSH* to immature granulosa cells caused rapid nuclear import of C subunit within 1 h. Nuclear C subunit decreased by 6 h after *FSH* but could be rapidly reimported to the nucleus by the addition of forskolin at 6, 24, or 48 h. Nuclear C subunit was associated with the rapid but transient increases in phospho-CREB. *FSH* *induced* Sgk in a biphasic manner in which the protein was nuclear at 1 h and cytoplasmic at 48 h. Aromatase mRNA was only expressed at 24-48 h after *FSH* , a pattern that was not altered by phosphodiesterases or phosphatases. In the luteinized (PO/hCG) granulosa cells, immunoreactive C subunit was localized in a punctate pattern in the nucleus as well as to a cytoplasmic basket-like structure, a distribution pattern not altered by forskolin. Aromatase, Sgk, and phospho-CREB were expressed at elevated levels in a non-forskolin-responsive manner. Most notable, both phospho-CREB and Sgk were preferentially localized in a punctate pattern within the cytoplasm and not altered by forskolin. Collectively, these data indicate that when granulosa cells differentiate to luteal cells the subcellular localization (nuclear vs. cytoplasmic) of A-kinase pathway components changes markedly. Thus, either the mechanisms of nuclear import and export or the presence of distinct docking sites (and functions ?) dictate where A-kinase, phospho-CREB and Sgk are localized in granulosa cells compared with the terminally differentiated luteal cells.

5/3,AB/18
DIALOG(R)File 155:MEDLINE(R)

10364157 99360581 PMID: 10433199
Effect of prolactin on the *expression* of luteinizing hormone receptors during cell differentiation in cultured rat granulosa cells.
Hirakawa T; Minegishi T; Tano M; Kameda T; Kishi H; Ibuki Y; Mizutani T; Miyamoto K
Department of Obstetrics and Gynecology School of Medicine, Gunma University, Maebashi, Japan. tminegis@sb.gunma-u.ac.jp
Endocrinology (UNITED STATES) Aug 1999, 140 (8) p3444-51, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Chronic and transient hyperprolactinemia has been associated with luteal phase dysfunction. Recently, evidence has emerged to suggest that elevated PRL may exert its antigonadal effects through reducing available ovarian LH receptors. We have now examined the influences of PRL on LH receptor *induction* in cultured granulosa cells. Basal specific LH binding was negligible and remained unchanged in response to treatment with PRL by itself. Whereas treatment with *FSH* produced, as expected, a substantial increase in specific LH binding, concurrent treatment with PRL resulted in no significant change during the first 4 days of culture, followed by a significant decrease in LH binding on days 5 and 6 as well as an approximately 50% inhibition of *FSH* effect on day 6. Scatchard plot analysis showed that concurrent treatment with PRL resulted in inhibition of the granulosa cell LH binding capacity, whereas no difference could be detected in the binding affinity of LH to its receptor. Treatment with 8-bromo-cAMP produced a significant increase in specific LH binding; concurrent treatment with PRL (30 ng/ml) produced a significant attenuation of 8-bromo-cAMP action. In addition, treatment with *FSH* increased the intracellular accumulation of cAMP, and concurrent treatment with PRL did not result in inhibition of the *FSH* action, as assessed by the generation of intracellular cAMP. Taken together, these findings suggest that the ability of PRL to

interfere with *FSH* action with regard to the *induction* of LH receptors is exerted at sites distal to those involved in cAMP generation. The effect of PRL on LH receptor messenger RNA (mRNA) levels was not significant during the increase in receptors, whereas after the maximal level of receptor *expression* was reached, the effect of PRL was apparent. Cotreatment with *FSH* (30 ng/ml) and increasing doses of PRL inhibited the levels of *FSH*-*induced* LH receptor mRNA in a dose-dependent manner, whereas PRL did not inhibit the effect of *FSH* on the *FSH* receptor mRNA. To investigate the hormonal regulation of the 5'-flanking region, we analyzed the effect of *FSH* on 1379 bp of LH receptor promoter in rat granulosa cells. Treatment with *FSH* (1-100 ng/ml) significantly enhanced the activity of 1379 bp of the LH receptor 5'-flanking region in dose-dependent manner. Treatment with 30 ng/ml PRL alone did not significantly influence the activity of the LH receptor promoter and did not affect the increased promoter activity *induced* by *FSH*. In addition, the rates of LH receptor mRNA gene transcription assessed by nuclear run-on transcription assay increased by the addition of *FSH* and were not affected by the addition of PRL in the presence of *FSH*. These data showed that PRL might not effect LH receptor gene transcription in the regulation of LH receptor mRNA. Next, an attempt was made to determine the effect of PRL on LH receptor mRNA stability by measuring the decay of LH receptor mRNA under conditions known to inhibit transcription. However, inhibitors of transcription were found to have a stabilizing effect on the LH receptor mRNA, thus potentially masking the effect of PRL. According to the *expression* of LH receptor mRNA, PRL might not affect the maximum level *induced* by *FSH*, but thereafter the maximum levels of LH receptor mRNA decreased faster than those of the control. Therefore, it may be possible that PRL acts to stimulate labile LH receptor mRNA-destabilizing factors.

5/3,AB/19
DIALOG(R)File 155:MEDLINE(R)

10250184 99227117 PMID: 10209256
Regulation of cAMP responsive element binding modulator isoforms in cultured rat ovarian granulosa cells.
Kameda T; Mizutani T; Minegishi T; Ibuki Y; Miyamoto K
Biosignal Research Center Institute for Molecular and Cellular Regulation, Gunma University, Maebashi, Gunma 371-8512, Japan. Biochimica et biophysica acta (NETHERLANDS) Apr 14 1999, 1445 (1) p31-8, ISSN 0006-3002 Journal Code: 0217513
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A pituitary glycoprotein hormone *FSH* stimulates ovarian granulosa cells to induce ovarian follicular development. In this study we identified rat ovarian genes that were rapidly *induced* by *FSH* in the cultured rat granulosa cells by means of subtraction cloning. Complementary DNA clones encoding cAMP responsive element binding modulator (CREM) were identified as one of the *FSH* inducible genes. Northern blotting and reverse transcription and polymerase chain reaction (RT-PCR) analyses revealed that only the repressor type of CREM gene products, ICER (inducible cAMP early repressor) isoforms, were *induced* by *FSH* treatment in cultured rat granulosa cells. The *induction* of ICER by *FSH* was mimicked by reagents known to increase intracellular cAMP levels, indicating that the *induction* is through cAMP and protein kinase A signal transduction system. *Induction* of ICER was also confirmed as the protein levels. Electrophoretic mobility shift assay of granulosa cell extracts with a radiolabeled double stranded oligonucleotide corresponding to somatostatin cAMP responsive element also revealed that only the ICER proteins were *induced* by *FSH* treatment, whereas levels of CREM proteins were nearly constant regardless of the *FSH* treatment. Our present study demonstrates that *FSH*-*induced* and cAMP-mediated *induction* and attenuation of transcriptional responses by CREM gene products may be a key mechanistic component for the granulosa cell differentiation and proliferation.

5/3,AB/20
DIALOG(R)File 155:MEDLINE(R)

10138567 99103897 PMID: 9886947
Biological roles of angiotensin II via its type 2 receptor during rat follicle atresia.
Kotani E; Sugimoto M; Kamata H; Fujii N; Saitoh M; Usuki S; Kubo T; Song K; Miyazaki M; Murakami K; Miyazaki H
Department of Obstetrics and Gynecology, Institute of Clinical Medicine, University of Tsukuba, Ibaraki 305-8572, Japan.
American journal of physiology (UNITED STATES) Jan 1999, 276 (1 Pt 1) pE25-33, ISSN 0002-9513 Journal Code: 0370511
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Type 1 angiotensin II (ANG II) receptors play crucial roles in the regulation of blood pressure and fluid osmolarity, whereas the physiological roles of type 2 ANG II receptors (AT2) remain unclear. Because AT2 is expressed in atretic follicles where granulosa cells undergo apoptosis, we examined the space and time relationship between AT2 *expression* and follicle atresia in vivo and the effect of AT2 on follicle-stimulating hormone (*FSH*) actions in vitro. Binding studies, autoradiography, and RT-PCR of AT2 revealed that the AT2 content in granulosa cells was time dependently increased at both protein and mRNA levels in equine chorionic gonadotropin-treated immature female rats. This increase paralleled the progression of atresia. ANG II suppressed *FSH* -caused prevention of DNA fragmentation, increases in luteinizing hormone receptor content, and estrogen production through AT2 in cultured granulosa cells. Moreover, *FSH*-*induced* stimulation of extracellular signal-regulated kinase activity, critical for cell survival, was inhibited by AT2 stimulation. These results suggest that AT2 mediates the progression of follicle atresia through granulosa cell apoptosis by inhibiting *FSH* actions.

5/3,AB/21
DIALOG(R)File 155:MEDLINE(R)

10068548 99047422 PMID: 9828191
Factors affecting the developmental competence of mouse oocytes grown in vitro: follicle-stimulating hormone and insulin.
Eppig J J; O'Brien M J; Pendola F L; Watanabe S
The Jackson Laboratory, Bar Harbor, Maine 04609-1500, USA. jje@jax.org Biology of reproduction (UNITED STATES) Dec

1998, 59 (6) p1445-53, ISSN 0006-3363 Journal Code: 0207224
Contract/Grant No.: CA34196; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

This study was undertaken to test the hypothesis that *FSH* treatment of cultured oocyte-granulosa cell complexes promotes acquisition of competence to complete preimplantation embryo development. Oocyte-granulosa cell complexes were isolated from the preantral follicles of 12-day-old mice and cultured for 10 days in serum-free medium, supplemented with insulin (5 microgram/ml), transferrin (5 microgram/ml), and selenium (5 ng/ml) and containing a highly potent preparation of *FSH* (0-5 ng/ml). Oocytes were matured and fertilized in vitro and embryos cultured to determine the frequency of development to the blastocyst stage. There was no effect of *FSH* on oocyte size, general morphology, or competence to resume meiosis. However, addition of *FSH* to medium containing insulin had a deleterious effect on the percentage of mature oocytes competent to develop to the blastocyst stage. Deletion of insulin from the medium for culture of oocyte-granulosa cell complexes prevented the deleterious effect of *FSH*, but *FSH* still did not promote acquisition of competence to complete preimplantation development. Culture of oocyte-granulosa cell complexes with *FSH* resulted in elevated *expression* of LH receptor (LHR) mRNA by granulosa cells and stimulated the production of functional LHRs, whether or not insulin was present. However, *FSH*- *induced* *expression* of LHR mRNA reached a maximum steady-state level by 4 days of culture in the presence of insulin, but this level was not reached until 10 days of culture without insulin. Granulosa cells encompassing growing mouse oocytes in vivo do not express LHR mRNA. Thus, *expression* of LHR mRNA by granulosa cells closely associated with growing oocytes in vitro indicates inappropriate or ambiguous development. In conclusion, conditions occurring during oocyte growth can have profound detrimental effects on oocyte developmental competence to complete preimplantation development, even when oocyte growth, general morphology, and competence to resume meiosis appear unaffected.

5/3,AB/22
DIALOG(R)File 155:MEDLINE(R)

09887482 98322730 PMID: 9658594
Hormonal and photoperiodic modulation of testicular mRNAs coding for inhibin/activin subunits and follistatin in Clethrionomys glareolus, Schreber.
Tahka K M; Kaipia A; Toppari J; Tahka S; Tuuri T; Tuohimaa P
Department of Biosciences, University of Helsinki, Finland.
Journal of experimental zoology (UNITED STATES) Jul 1 1998, 281 (4) p336-45, ISSN 0022-104X Journal Code: 0375365
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Photoperiodic and hormonal modulation of mRNAs for testicular inhibin/activin subunits and follistatin were studied in a seasonally breeding rodent, the bank vole (Clethrionomys glareolus). Photoperiod- *induced* testicular regression had no effect on the relatively low steady-state levels of follistatin mRNA. Inhibin alpha (I alpha) and beta B (I beta B) mRNA levels were significantly higher in regressed than in active gonads, but inhibin beta A was undetectable. The effect of gonadotropin administration on testicular weight and mRNA concentrations differed between the sexually active and quiescent voles. Neither *FSH* (1.2 U/kg; s.c. for 5 days) nor hCG (600 IU/kg; s.c. for 5 days) affected testicular weight in sexually active voles, whereas both gonadotropins significantly increased testicular weight in photo-regressed individuals. *FSH* had no effect on I alpha or I beta B mRNA concentrations in the active testes, whereas excessive hCG challenge *induced* a decrease in the steady-state levels of these mRNAs. *FSH* *induced* an increase in I alpha mRNA concentrations in the regressed gonad, whereas both gonadotropins concomitantly down-regulated I beta B mRNA levels. In conclusion, the high *expression* of I alpha and I beta B mRNA in the regressed testis imply autocrine and paracrine roles for inhibin/activin in the quiescent gonad of seasonal breeders. Inhibin alpha-subunit *expression* is at least partly under the control of *FSH* in the bank vole testis.

5/3,AB/23
DIALOG(R)File 155:MEDLINE(R)

09719208 98152085 PMID: 9491385
Mouse oocytes suppress cAMP-*induced* *expression* of LH receptor mRNA by granulosa cells in vitro.
Eppig J J; Pendola F L; Wigglesworth K
Jackson Laboratory, Bar Harbor, Maine 04609, USA. jje@aretha.jax.org
Molecular reproduction and development (UNITED STATES) Mar 1998, 49 (3) p327-32, ISSN 1040-452X Journal Code: 8903333
Contract/Grant No.: CA34196; CA; NCI; HD23839; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Mouse oocytes suppress follicle-stimulating hormone (*FSH*)- *induced* luteinizing hormone receptor (LHR) messenger ribonucleic acid (mRNA) *expression* in cultured granulosa cells. The objective of this study was to assess the mechanism by which oocytes suppress *FSH*- *induced* LHR *expression*. The effect of cumulus cell-denuded, germinal-vesicle-stage oocytes, isolated from antral follicles, on *FSH*-*induced* cyclic adenosine monophosphate (cAMP) production by cultured granulosa cells was determined by radioimmunoassays. In addition, the effect of oocytes on 8Br-cAMP-*induced* LHR mRNA steady-state *expression* by granulosa cells was assessed by RNase protection assays. Oocytes had no detectable effect on *FSH*-*induced* cAMP production. However, oocytes dramatically suppressed 8Br-cAMP-*induced* LHR mRNA steady-state *expression* by granulosa cells. It was concluded that the mechanism by which oocytes suppress *FSH*- *induced* steady-state *expression* of LHR mRNA is not by inactivating *FSH*, preventing functional interactions of *FSH* with its granulosa cell receptors, or by interfering with the signal-transduction mechanisms required for *FSH* -dependent cAMP production. In addition, since oocytes suppressed the 8Br-cAMP- *induced* increase in steady-state *expression* of mRNA for LHR, oocyte-derived factors probably suppress *expression* by acting downstream of *FSH*-*induced* elevation of granulosa cell cAMP.

5/3,AB/24

DIALOG(R)File 155:MEDLINE(R)

09712339 98149667 PMID: 9490023
The effect of activin and *FSH* on the differentiation of rat granulosa cells.
Kishi H; Minegishi T; Tano M; Kameda T; Ibuki Y; Miyamoto K
Department of Obstetrics and Gynecology, Gunma University School of Medicine, Gunma University, Maebashi, Japan.
FEBS letters (NETHERLANDS) Jan 30 1998, 422 (2) p274-8, ISSN 0014-5793 Journal Code: 0155157
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The differentiation of granulosa cells is regulated by follicle-stimulating hormone (*FSH*) and local ovarian factors. To further analyze the role of *FSH* and activin in this process, we have examined the effect of *FSH* and activin on *FSH* and luteinizing hormone/human chorionic gonadotropin (LH/hCG) receptor *induction* in granulosa cells. Granulosa cells from diethylstilbestrol (DES)-primed immature rats produce activin and maintain *FSH* receptor without LH/hCG receptor *expression* in the absence of *FSH*. On the other hand, *FSH* *induced* granulosa cells to differentiate into more mature granulosa cells in which higher LH/hCG receptor *expression* and diminished activin production were observed.

5/3,AB/25
DIALOG(R)File 155:MEDLINE(R)

09605103 98022426 PMID: 9359468
Transforming growth factor-alpha stimulates insulin-like growth factor binding protein-4 (IGFBP-4) *expression* and blocks follicle-stimulating hormone regulation of IGFBP-4 production in rat granulosa cells.
Piferrer F; Li D; Shimasaki S; Erickson G F
Department of Reproductive Medicine, University of California, San Diego, La Jolla 92093-0674, USA.
Molecular and cellular endocrinology (IRELAND) Sep 30 1997, 133 (1) p9-17, ISSN 0303-7207 Journal Code: 7500844
Contract/Grant No.: HD-29008; HD; NICHD; HD-30308; HD; NICHD Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The ability of TGF-alpha to regulate insulin-like growth factor binding protein-4 (IGFBP-4), was investigated. Primary cultures of rat granulosa cells (GC) were grown in serum-free medium with rat (r) TGF-alpha and/or rFSH, and secreted IGFBP-4 protein and its steady state mRNA levels were measured by Western immunoblotting and Northern blotting, respectively. Control (untreated) cells secreted IGFBP-4 spontaneously, and the levels were increased by rTGF-alpha in a dose- and time-dependent manner. rTGF-alpha abolished *FSH*-*induced* IGFBP-4 protease activity and suppressed *FSH*-dependent effects on IGFBP-4 production. IGFBP-4 mRNA levels were decreased and increased by *FSH* and TGF-alpha, respectively, and TGF-alpha blocked the *FSH* effects. These results demonstrate that TGF-alpha is a potent stimulator of IGFBP-4 *expression* in rat GC and can overcome the regulatory effects of *FSH* on IGFBP-4 production. The consequence of these TGF-alpha effects is a marked, sustained increase in the levels of IGFBP-4 in the microenvironment.

5/3,AB/26
DIALOG(R)File 155:MEDLINE(R)

09594710 98003881 PMID: 9410365
[Role of tumor necrosis factor in the male gonad]
Role du tumor necrosis factor dans la gonade male.
Benahmed M
Inserm Unite 407, Laboratoire de Biochimie, Bat. 3B, Centre Hospitalier Lyon-Sud, Pierre-Benite.
Contraception, fertilite, sexualite (1992) (FRANCE) Jul-Aug 1997, 25 (7-8) p569-71, ISSN 1165-1083 Journal Code: 9314045
Document type: Journal Article; Review; Review, Tutorial ; English Abstract
Languages: FRENCH
Main Citation Owner: NLM
Record type: Completed
Within the male gonad, TNF alpha is secreted by macrophages in the interstitial tissu and by germ cells in seminiferous tubules. TNF alpha receptors (type I) have been detected in the somatic cells of the testis (i.e. Leydig and Sertoli cells). TNF alpha has two type of action within the testis: the cytokine has an anti-hormonal role and play a role in the interactions between Sertoli and germ cells. Anti-hormonal actions of TNF alpha are (i) inhibition of LH-*induced* testosterone production in Leydig cells and (ii) inhibition of *FSH*-*induced* inhibin production in Sertoli cells. Moreover, TNF alpha; produced by germ cells, enhanced *expression* of growth factors in Sertoli cells (IGFBP3, receptor type I of bFGF) and enhanced production of energetic metabolite important for germ cells such as lactate (via enhancement of lactate dehydrogenase enzyme, isoform 5). Moreover, Fas/Fas ligand system, proteins related to TNF alpha, seem to play a key role in the protection of germ cells against the immune system within the testis. In conclusion, TNF alpha and related proteins, could play a great role in testicular functions such as spermatogenesis (interactions between Sertoli and germ cells) and in the interactions between immune system and spermatogenesis (role of TNF alpha originating form blood/testicular macrophages, role of Fas/Fas ligand system).

5/3,AB/27
DIALOG(R)File 155:MEDLINE(R)

09453653 97338913 PMID: 9195473
Cloning, sequencing and in vitro functional *expression* of recombinant donkey follicle-stimulating hormone receptor: a new insight into the binding specificity of gonadotrophin receptors.
Richard F; Martinat N; Remy J J; Salesse R; Combarnous Y
Unite Recepteurs et Communication Cellulaire, Batiment des Biotechnologies, Institut National de la Recherche Agronomique, Jouy-en-Josas, France.
Journal of molecular endocrinology (ENGLAND) Jun 1997, 18 (3) p193-202, ISSN 0952-5041 Journal Code: 8902617
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Among all mammalian *FSH* receptors (*FSH*-R; including donkey (dk) *FSH*-R), only horse (hs) *FSH*-R does not bind hsLH/chorionic gonadotrophin (CG). In order to delineate the

structural origin of hsFSH-R specificity precisely, we have cloned dkFSH-R cDNA from donkey testis mRNA by RT-PCR. Transiently expressed dkFSH-R endowed COS-7 cells with both hsLH/CG- and *FSH*-binding activity, as well as *FSH*-*induced* cAMP production. The deduced dkFSH-R amino acid sequence shares 96% identity with the hsFSH-R: notably, in the hormone-binding domain, the specificity of hsFSH-R may be ascribed to only four divergent amino acids: Thr 173, Asp 202, Asn 268 and Pro 322. Interestingly, hsAsn 268 could bear an additional N-glycosylation. According to receptor negative specificity, these amino acids could be implicated in preventing LH/CG binding to *FSH*-R.

5/3,AB/28
DIALOG(R)File 155:MEDLINE(R)

09368675 97251199 PMID: 9096881
Murine oocytes suppress *expression* of luteinizing hormone receptor messenger ribonucleic acid by granulosa cells.
Eppig J J; Wigglesworth K; Pendola F; Hirao Y
Jackson Laboratory, Bar Harbor, Maine 04609-1500, USA. jje@aretha.jax.org Biology of reproduction (UNITED STATES) Apr 1997, 56 (4) p976-84, ISSN 0006-3363 Journal Code: 0207224
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
This study tested the hypothesis that murine oocytes participate in the establishment of granulosa cell phenotypic heterogeneity in preovulatory follicles. In these follicles, mural granulosa cells express LH receptors (LHR) and LHR mRNA, but *expression* of these molecules is low or undetectable in cumulus cells. Thus, the *expression* of LHR mRNA is a marker of the mural granulosa cell phenotype in preovulatory follicles. Cumulus cells expressed elevated steady-state levels of LHR mRNA when oocytes were microsurgically removed from oocyte-cumulus cell complexes, and this was prevented by paracrine factor(s) secreted by isolated oocytes. These factors also suppressed *FSH*-*induced* elevation of the level of LHR mRNA *expression* by mural granulosa cells isolated from small antral follicles, even when *expression* was augmented by culturing granulosa cells on components of basal lamina. Moreover, factor(s) secreted by oocytes suppressed the *expression* of LHR mRNA in mural granulosa cells isolated from preovulatory follicles already expressing elevated levels of these transcripts. The ability of oocytes to suppress the LHR mRNA *expression* by granulosa cells was developmentally regulated. Oocytes from preantral follicles and mature (metaphase II arrested) oocytes were less effective in suppressing *expression* than fully grown, germinal vesicle (GV)-stage oocytes. Furthermore, two-cell-stage embryos did not suppress LHR mRNA levels. Coculture of isolated oocytes with granulosa cells affected the synthesis of very few granulosa cell proteins detected by fluorography of two-dimensional gels after 35S-methionine labeling. Thus, oocyte suppression of *FSH*-*induced* LHR mRNA *expression* is specific in both the suppressing cell type and the effects on granulosa cells. It is concluded that the default pathway of granulosa cell differentiation produces the mural granulosa cell phenotype, as represented by the *expression* of LHR mRNA. This pathway is abrogated by oocytes. Thus, oocytes play a dominant role in establishing the fundamental heterogeneity of the granulosa cell population of preovulatory follicles.

5/3,AB/29
DIALOG(R)File 155:MEDLINE(R)

09245830 97131943 PMID: 8977400
Induction of guanosine triphosphate-cyclohydrolase by follicle-stimulating hormone enhances interleukin-1 beta-stimulated nitric oxide synthase activity in granulosa cells.
Tabraue C; Diaz Penate R; Gallardo G; Hernandez I; Quintana J; Lopez Blanco F; Gonzalez Reyes J; Fanjul L F; Ruiz de Galarreta C M Department of Biochemistry Molecular Biology and Physiology, University of Las Palmas School of Medicine, Spain.
Endocrinology (UNITED STATES) Jan 1997, 138 (1) p162-8, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In cultured granulosa cells, interleukin-1 beta (IL-1 beta) *induced* a time-dependent (16-72 h) and dose-related (0.3-30 ng/ml) stimulation of nitric oxide (NO) synthase (NOS) activity, as determined by the catalytic conversion of [3H]arginine to [3H]citrulline and NO2- accumulation in the culture medium. Although *FSH* alone failed to stimulate NOS activity, concomitant treatment with the gonadotropin (200 ng/ ml) or the cell-permeant cAMP analog (Bu)2cAMP (0.5 mM) markedly enhanced IL-1 beta- *induced* NO generation in cultured granulosa cells. The effect of IL-1 beta on citrulline biosynthesis and NO2- accumulation was abrogated by the NOS inhibitor NG-methyl-L-arginine or the IL-1-receptor antagonist protein. In contrast bacterial endotoxin (lipopolysaccharide), interferon-gamma, or tumor necrosis factor-alpha, which are well known inducers of inducible NOS (iNOS) in a variety of immunocompetent and nonimmunocompetent cell types, failed to increase [3H]citrulline formation or NO2- accumulation in untreated or *FSH* -stimulated cells. As demonstrated by reverse transcriptase-PCR analysis, IL-1 beta-stimulated NO generation was accompanied by a time-dependent increase in messenger RNA levels for iNOS and GTP-cyclohydrolase (GTPCH), the rate-limiting step for de novo tetrahydrobiopterin (BH4) biosynthesis. Treatment with *FSH* augmented only GTPCH messenger RNA *expression*, and a more than additive GTPCH signal was observed when cells were simultaneously challenged with IL-1 beta and *FSH* . Treatment with the GTPCH inhibitor 2,4-diamino-6-hydroxypyrimidine prevented IL-1 beta-*induced* NOS activity in untreated or *FSH*-stimulated cells, and this inhibition was completely reversed by sepiapterin, a substrate for BH4 biosynthesis, via an alternative pterin salvage pathway present in many cell types. As BH4 is an essential cofactor for NOS catalytic activity, these observations strongly suggest that *FSH*-*induced* biosynthesis of endogenous BH4 is essential for full iNOS biosynthetic capacity in IL-1 beta-stimulated granulosa cells.

5/3,AB/30
DIALOG(R)File 155:MEDLINE(R)

09170834 97080483 PMID: 8921828
Presence and localization of endothelin receptor in the rat ovary and its regulation by pituitary gonadotropins.

Otani H; Yamoto M; Fujinaga H; Nakano R

Department of Obstetrics and Gynecology, Wakayama Medical College, Japan. European journal of endocrinology / European Federation of Endocrine Societies (NORWAY) Oct 1996, 135 (4) p449-54, ISSN 0804-4643 Journal Code: 9423848

Comment in Eur J Endocrinol. 1996 Oct;135(4) 391-3; Comment in PMID 8921818

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

In the present study we examined the regulation of receptors for endothelin 1 (ET-1) in rat granulosa cells. We examined the localization and regulation of ET receptors in immature rat ovary and the effects of ET-1 on steroidogenesis in cultured rat granulosa cells. The ovaries used in autoradiography were derived from pregnant mare serum gonadotropin and human chorionic gonadotropin-treated immature rats. Granulosa cells were obtained from diethylstilbestrol-treated immature rats and incubated with 125I-ET-1. Granulosa cells were cultured with ET-1 in the presence or absence of ovine follicle-stimulating hormone. The concentrations of sex steroid hormones in conditioned media were measured by radioimmunoassay. The binding site for ET-1 was localized in the granulosa cells, but not in thecal and luteal cells. Follicle-stimulating hormone (*FSH*) *induced* a dose-dependent increase in specific binding for ET-1 to cultured rat granulosa cells. In contrast, luteinizing hormone (LH) *induced* a dose-dependent decrease in specific binding for ET-1 to cultured rat granulosa cells. Conversely, treatment with prolactin and several sex steroid hormones had no effects on the specific binding of ET-1. Treatment with ET-1 inhibited *FSH*-stimulated accumulation of progesterone and estradiol in cultured rat granulosa cells. The results indicate that both *FSH* and LH influence the *expression* of ET-1 receptor, and that ET-1 may play a regulatory role in the ontogeny of the granulosa cell.

5/3,AB/31

DIALOG(R)File 155:MEDLINE(R)

09058025 96426206 PMID: 8828500

Androgen receptor gene *expression* in rat granulosa cells: the role of follicle-stimulating hormone and steroid hormones.

Tetsuka M; Hillier S G

Department of Obstetrics and Gynecology, University of Edinburgh, United Kingdom.

Endocrinology (UNITED STATES) Oct 1996, 137 (10) p4392-7, ISSN 0013-7227 Journal Code: 0375040

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

In rat ovary, androgen receptor (AR) is predominantly expressed in granulosa cells and is developmentally regulated. However, the exact mechanism that is responsible for the regulation of AR in granulosa cells has not been elucidated. The aim of this study was to examine 1) the levels of AR messenger RNA (mRNA) *expression* in granulosa cells from follicles of different size and 2) the effects of *FSH*, 8-bromo-cAMP, androgen, and estrogen on AR mRNA levels in granulosa cells in vitro. The abundance of AR mRNA was examined by ribonuclease protection assay using 32P-labeled AR complementary RNA probe and related to that of P450aromatase (P450arom) mRNA, a well established maker of granulosa cell differentiation. In large follicles (> 400 microns in diameter), the abundance of AR mRNA was decreased to 51% of that in small follicles (< 200 microns; P < 0.01), whereas the abundance of P450arom mRNA increased to 277% (P < 0.01). In medium follicles (200-400 microns), the abundance of AR mRNA was maintained (101%), whereas the abundance of P450arom mRNA increased to 202% of that in small follicles (P < 0.05). Treatment with *FSH* (0-300 ng/ml) or 8-bromo-cAMP (0-4 mM) *induced* P450arom mRNA in the cultured granulosa cells in a dose-dependent manner; however, it did not affect the levels of AR mRNA *expression*. Treatment with 5 alpha-dihydrotestosterone (1 microM) resulted in a significant reduction in the abundance of AR mRNA to 67% of the control value (P < 0.05). This effect was reversed by the addition of *FSH* (100 ng/ml; P < 0.01). Treatment with diethylstilbestrol (1 microM), alone or in combination with *FSH* (100 ng/ml), did not have any significant effect, although these treatments tended to decrease the abundance of AR mRNA to 81% and 85%, respectively. Both 5 alpha-dihydrotestosterone and diethylstilbestrol dramatically enhanced the abundance of *FSH*-*induced* P450arom mRNA compared to the effect of *FSH* alone. These results indicate that 1) the down-regulation of AR mRNA *expression* takes place in granulosa cells of preovulatory follicles; 2) *FSH* is not directly responsible for this event; and 3) androgen down-regulates AR mRNA *expression* in immature granulosa cells, and this effect is reversed by *FSH*. We conclude that androgen and *FSH* jointly regulate AR mRNA *expression* in rat granulosa cells.

5/3,AB/32

DIALOG(R)File 155:MEDLINE(R)

09054688 96432327 PMID: 8835393

Transcriptional regulation of sertoli cell differentiation by follicle-stimulating hormone at the level of the c-fos and transferrin promoters.

Chaudhary J; Whaley P D; Cupp A; Skinner M K

Reproductive Endocrinology Center, University of California, San Francisco 94143-0556, USA.

Biology of reproduction (UNITED STATES) Mar 1996, 54 (3) p692-9, ISSN 0006-3363 Journal Code: 0207224

Contract/Grant No.: HD 20583; HD; NICHD

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

One of the primary endocrine hormones that influence the onset of Sertoli cell differentiation at puberty and help maintain differentiation in the adult testis is *FSH*. *FSH* can modulate the majority of Sertoli cell differentiated functions, including stimulation of the iron-binding protein transferrin. Previous studies have shown that *FSH* alters the levels of cAMP and the immediate early gene c-fos. The current study was designed to investigate the transcriptional regulation of Sertoli cell differentiation by examining the actions of *FSH* on the promoter of the immediate early gene c-fos and the promoter of the downstream differentiated function gene transferrin. The regulation of c-fos by *FSH* was investigated with various chloramphenicol acetyltransferase (CAT) constructs containing segments of the c-fos promoter, such as the serum response element (SRE), cAMP response element (CRE), and AP1/phorbol ester/TPA response element (TRE), that were transfected

into cultured Sertoli cells. Observations indicate that *FSH* can stimulate all three response elements, as well as a whole c-fos promoter construct. Interestingly, *FSH* was found to have a more dramatic effect on the SRE-CAT than a cAMP analog, suggesting a difference in the actions of the two agents. Gel mobility shift assays were performed to confirm the reporter gene results. Nuclear extracts of *FSH*-stimulated Sertoli cells caused a labeled AP1 oligonucleotide to form a DNA/protein complex (i.e., gel shift), indicating activation of the c-fos gene and binding of the c-fos/jun complex. Nuclear extracts from both *FSH* - and cAMP-stimulated Sertoli cells promoted similar gel shifts with SRE and CRE oligonucleotides. This observation supports the reporter gene data in indicating that *FSH* can influence both the SRE and CRE. A gel mobility shift assay was also performed with an oligonucleotide containing the 5'-flanking ETS domain of the SRE (ETS-SRE) that allows the formation of a ternary complex. *FSH*-stimulated Sertoli cell nuclear extracts were found to promote a unique ETS-SRE gel shift not present in cAMP-stimulated cells. The observations imply that *FSH* actions on the SRE are in part distinct from the actions of cAMP. Transferrin gene *expression* was examined to study the downstream regulation of Sertoli cell differentiation. CAT constructs containing deletion mutants of a 3-kb mouse transferrin promoter were used. When transfected into Sertoli cells, the 581-bp transferrin minimal promoter, previously shown to contain a CRE, had a significant response to cAMP and *FSH*. The 1.6-, 2.6-, and 3-kg transferrin promoter constructs also responded to *FSH* and cAMP to the same extent as, or to a lesser extent than, the 581-bp minimal promoter. Interestingly, the actions of *FSH* on the 581-bp minimal transferrin promoter were more dramatic than those of cAMP. The importance of *FSH* -*induced* c-fos in the regulation of transferrin *expression* was demonstrated in the current study when a c-fos antisense oligonucleotide was found to partially inhibit (50%) the ability of *FSH* to induce the *expression* of a transferrin promoter (CAT) construct. Therefore, *FSH* appears to act through multiple transcriptional activation pathways. The first involves cAMP and the CRE at both early-event genes (e.g., c-fos) and downstream genes (e.g., transferrin). It is likely that other pathways involve alternate signal transduction events (e.g., calcium mobilization) and promoter response elements (e.g., SRE). These multiple pathways may act in a compensatory manner to assure the ability of *FSH* to influence Sertoli cell differentiation and/or in a synergistic manner to amplify *FSH* actions.

5/3,AB/33
DIALOG(R)File 155:MEDLINE(R)

08812050 96174909 PMID: 8592519
A role for increased lutropin/choriogonadotropin receptor (LHR) gene transcription in the follitropin-stimulated *induction* of the LHR in granulosa cells.
Shi H; Segaloff D L
Department of Physiology, University of Iowa College of Medicine, Iowa City 52242, USA.
Molecular endocrinology (Baltimore, Md.) (UNITED STATES) Jun 1995, 9 (6) p734-44, ISSN 0888-8809 Journal Code: 8801431
Contract/Grant No.: DK-25295; DK; NIDDK; HD-00968; HD; NICHD; HD-22196; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Follitropin (*FSH*) has been shown in previous studies to stimulate the *induction* of the LH/CG receptor (LHR) and LHR mRNA in the granulosa cells of diethylstilbesterol-primed immature rats. The present studies were undertaken to identify the mechanisms underlying the hormone-dependent *induction* of the LHR in rat granulosa cells. The effect of *FSH* on LHR mRNA stability was determined by measuring the decay of LHR mRNA after removal of *FSH* under conditions where transcription was inhibited. Under these conditions, readdition of *FSH* had little effect on mRNA stability. However, inhibitors of transcription themselves were found to have a marked effect on stabilizing the LHR mRNA, thus potentially masking an effect of *FSH*. These results suggest that there is a labile destabilizing factor that constitutively degrades LHR mRNA. At present, it cannot be ascertained whether *FSH* has any effect on this destabilizing factor. Transcriptional activity of the LHR gene was examined using nuclear run-on assays. It was found that 1) in the absence of *FSH*, LHR-binding activity and mRNA levels were negligible, but the LHR gene was transcriptionally active in granulosa cells of immature rats; 2) incubations of granulosa cells with *FSH* or 8-bromo-cAMP significantly increased endogenous LHR gene transcription (approximately 10-fold) under conditions where increases in LHR mRNA were observed; 3) the continuous presence of *FSH* or 8-bromo-cAMP was required to maintain elevated levels of LHR gene transcription and LHR mRNA; and 4) exogenous estradiol alone had no effect on transcription of the LHR gene although it was able to synergistically enhance *FSH*-*induced* LHR *expression*. These experiments suggest that while the effects of estradiol on LHR *induction* do not appear to be mediated by an increase in LHR gene transcription, the effects of *FSH* (or cAMP) on LHR *induction* are clearly mediated, at least in part, by significant increases in the rate of LHR gene transcription.

5/3,AB/34
DIALOG(R)File 155:MEDLINE(R)

08765548 96111473 PMID: 8674825
Follicle-stimulating hormone regulates the *expression* of cyclic protein-2/cathepsin L messenger ribonucleic acid in rat Sertoli cells in a stage-specific manner.
Penttila T L; Hakovirta H; Mali P; Wright W W; Parvinen M
Department of Anatomy, University of Turku, Finland.
Molecular and cellular endocrinology (IRELAND) Sep 22 1995, 113 (2) p175-81, ISSN 0303-7207 Journal Code: 7500844
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Cyclic protein-2/cathepsin L (CP-2) is secreted by Sertoli cells in a highly stage-specific manner, maximally during stages VI-VII of the rat seminiferous epithelial cycle. We investigated *FSH* regulation of CP-2 mRNA *expression* of its cellular localization in isolated staged seminiferous tubular segments. *FSH* *induced* a significant increase of CP-2 mRNA *expression* and its cellular localization in isolated staged seminiferous tubular segments. *FSH* *induced* a significant increase of CP-2 mRNA levels in stages IX-I, whereas in stages

II-VIII, the levels of CP-2 mRNA were reduced. A similar effect was produced by two cAMP analogs, dbcAMP (0.2 mM) and Sp cAMP (20 microM). *FSH* and cAMP did not affect on the levels of SGP-2 mRNA during the seminiferous epithelial cycle. The magnitude of the response was time- and dose-dependent; the maximum was obtained with 100 ng/ml of *FSH*. It is likely that *FSH* regulates Cp-2 gene transcription, since de novo RNA synthesis was required for the stimulatory *FSH* effect on CP-2 mRNA levels, while ongoing protein synthesis was not. In conclusion, the data suggest that *FSH*, via cAMP-mediated pathway, regulates CP-2/cathepsin L gene transcription in rat Sertoli cells and modulated the stage-specific *expression* pattern.

5/3,AB/35
DIALOG(R)File 155:MEDLINE(R)

08634450 95393916 PMID: 7664681
Transforming growth factor-beta receptor type II *expression* in the hamster ovary: cellular site(s), biochemical properties, and hormonal regulation.
Roy S K; Kole A R
Leland J. And Dorothy H. Olson Center for Women's Health, Department of Obstetrics and Gynecology, University of Nebraska Medical Center, Omaha 68198-4515, USA.
Endocrinology (UNITED STATES) Oct 1995, 136 (10) p4610-20, ISSN 0013-7227 Journal Code: 0375040
Contract/Grant No.: HD-18165; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The hormonal regulation of transforming growth factor-beta (TGF beta) receptor type II (T beta RII) protein *expression* in the hamster ovary was evaluated by [125I]TGF beta 1 cross-linking, immunolocalization, and immunoprecipitation of T beta RII using receptor-specific antibodies. Granulosa cells of preantral and antral follicles, and interstitial and luteal cells showed strong signal on day 1 at 0900 h; interstitial and luteal staining was maximum. Immunoreactivity in the interstitium fell by day 2 and reappeared on day 4. A sharp reduction of immunostaining occurred after the gonadotropin surge. In hypophysectomized hamsters, *FSH* *induced* T beta RII in both granulosa and interstitial cells, but LH was effective only on interstitial cells. Whereas 17 beta-estradiol (17 beta E2) efficiently *induced* interstitial T beta RII, progesterone severely attenuated E2 *induction* of receptor protein. Apart from a membrane-associated form of T beta RII, a novel cytosolic form of T beta RII was detected. The cytosolic T beta RII is a glycoprotein with N'-linked oligosaccharides, like its membrane counterpart, possessing serine-threonine kinase activity that is TGF beta sensitive. The membrane-associated T beta RII disappeared on day 2 of the cycle, but reappeared by day 4 in the morning. A good correlation was found with the cytosolic form. Hypophysectomy diminished, whereas *FSH*, LH, and 17 beta E2 increased both forms of T beta RII; however, LH *induction* of the cytosolic form was greater than that by *FSH*. Progesterone prevented T beta RII protein integration to the membrane, but testosterone and dihydrotestosterone were also effective in T beta RII *induction* in the membrane. A high E2/progesterone ratio was an important determinant in T beta RII *induction* in the cell membrane. These results provide the first direct evidence for the presence of a functional T beta RII in the ovary. The receptor is a serine/threonine kinase and exists as distinct cytosolic and membrane forms that show a unique relationship during the estrous cycle. The *induction* of ovarian T beta RII is critically and temporally influenced by gonadotropins and ovarian steroid hormones.

5/3,AB/36
DIALOG(R)File 155:MEDLINE(R)

08596177 95354569 PMID: 7628357
Regulation of 3 beta-hydroxysteroid dehydrogenase delta 5/delta 4-isomerase and cholesterol side-chain cleavage cytochrome P450 by activin in rat granulosa cells.
Miro F; Smyth C D; Whitelaw P F; Milne M; Hillier S G
Department of Obstetrics and Gynecology, University of Edinburgh Center for Reproductive Biology, Scotland.
Endocrinology (UNITED STATES) Aug 1995, 136 (8) p3247-52, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Activin is a dimeric protein implicated in the local control of follicular steroidogenesis. Using cultured rat granulosa cells, we previously showed that the effect of activin on *FSH*-*induced* progesterone synthesis changes with preovulatory follicular development, from positive regulation in nondifferentiated (immature) granulosa cells to negative regulation in preovulatory (mature) granulosa cells. The aim of the present study was to assess development-related effects of activin on the *expression* of enzymes crucial to progesterone synthesis: cholesterol side-chain cleavage cytochrome P450 (P450scc) and 3 beta-hydroxysteroid dehydrogenase/delta 5-4-isomerase (3 beta HSD). Nondifferentiated granulosa cells were isolated from the ovaries of estrogen-pretreated immature female rats that received no other treatment; differentiated granulosa cells were obtained from similar animals treated for 48 h with human *FSH* to induce preovulatory follicular development. Cells were cultured for 48 h in serum-free medium with and without human *FSH* and/or recombinant activin-A, and medium was collected for measurement of progestagens (progesterone, pregnenolone, and 20 alpha-dihydroprogesterone). In cultures of nondifferentiated granulosa cells, activin augmented the *FSH*-*induced* production of all three steroids. In differentiated granulosa cells, activin suppressed the *FSH* -stimulated production of progesterone and 20 alpha-dihydroprogesterone, but had no effect on pregnenolone. The presence of exogenous pregnenolone increased the overall production of progesterone, but did not alter qualitative steroidogenic responses to activin. To assess the interaction between *FSH* and activin on 3 beta HSD and P450scc messenger RNA (mRNA) *expression*, Northern blot analyses were performed on total RNA isolated from cultured granulosa cells. Treatment in vitro with *FSH* alone markedly enhanced the abundance of both the 3 beta HSD and P450scc mRNA transcripts in nondifferentiated and differentiated granulosa cells. *FSH*-stimulated *expression* of P450scc mRNA was further enhanced by cotreatment of nondifferentiated granulosa cells with activin. However, activin had no consistent effect on *FSH*-stimulated *expression* of 3 beta HSD mRNA in nondifferentiated cells. In differentiated granulosa cells, both mRNAs were suppressed

more than 50% by the presence of activin. We conclude that the in vitro effects of activin on *FSH*-*induced* *expression* of 3 beta HSD and P450scc mRNAs in rat GC are similar: initially stimulatory (P450scc) or without effect (3 beta HSD), then becoming completely inhibitory. The mechanism of this development-dependent change in the granulosa cell response to activin remains to be elucidated.

5/3,AB/37
DIALOG(R)File 155:MEDLINE(R)

08594664 95352759 PMID: 7626723
Dual actions of phorbol ester on cytochrome P450 cholesterol side-chain cleavage messenger ribonucleic acid accumulation in porcine granulosa cells.
Lahav M; Garmey J C; Shupnik M A; Veldhuis J D
Department of Internal Medicine University of Virginia Health Sciences Center, Charlottesville 22908, USA.
Biology of reproduction (UNITED STATES) May 1995, 52 (5) p972-81, ISSN 0006-3363 Journal Code: 0207224
Contract/Grant No.: IK04 HD00634; HD; NICHD; P30-HD28934; HD; NICHD; RO1 HD16806; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In earlier studies in cultures of porcine granulosa cells prepared from small antral follicles, steroidogenesis-related loci were inhibited by treatment for 48 h with 12-O-tetradecanoyl-phorbol-13-acetate (TPA), a potent activator of protein kinase C (PKC). In the present investigation, cells were incubated in serum-free medium for 48 h, with various agents present during the last 2-24 h. With TPA at 30 ng/ml, the *FSH* -stimulated cAMP accumulation was markedly enhanced at all time points. *FSH* increased the concentration of cytochrome P450 cholesterol side-chain cleavage (P450scc) mRNA throughout the 24-h incubation. At 4 and 8 h, TPA increased the accumulation of P450scc mRNA, having an additive effect with *FSH*. However, at 24 h, TPA markedly suppressed the *FSH*-*induced* increased in P450scc mRNA. Pretreatment of cells with *FSH* did not shorten the time required for TPA to become inhibitory. The stimulatory effect of 8-bromo-cAMP on P450scc mRNA also was augmented by TPA at 4 h, but significant inhibition was not observed at 24 h. The concentration of glyceraldehyde-3-phosphate dehydrogenase mRNA, intended to be used for correction of gel loading, was stably increased by both cAMP and TPA. These effects of TPA suggest multiple actions of PKC(s) on the regulation of P450scc *expression* and other endpoints in ovarian granulosa cells.

5/3,AB/38
DIALOG(R)File 155:MEDLINE(R)

08560329 95317456 PMID: 7796938
Protein kinase C inhibition of in vitro *FSH*-*induced* differentiation in pig granulosa cells.
Hatey F; Mulsant P; Bonnet A; Benne F; Gasser F
Laboratoire de Genetique Cellulaire, Centre de Recherches de Toulouse, Institut National de la Recherche Agronomique, Castanet-Tolosan, France. Molecular and cellular endocrinology (IRELAND) Jan 1995, 107 (1) p9-16, ISSN 0303-7207 Journal Code: 7500844
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In granulosa cells, growth factor IGF I plays a major role in both growth and differentiation, acting through an autocrine/paracrine mechanism, and its production is regulated by *FSH*, via cyclic AMP (cAMP). As protein kinase C is also involved in granulosa cell function, we investigated the possibility that its activation could balance the positive effects of *FSH* . Using pig granulosa cells cultured in vitro, we studied the effects of protein kinase C activation by tetradecanoylphorbol acetate (TPA) on IGF I mRNA level. We also checked morphological modifications, cAMP production and steroidogenesis at the P450 side chain cleavage mRNA and progesterone levels. Our data demonstrate that protein kinase C activation antagonizes the in vitro *FSH*-*induced* differentiation, particularly morphological modifications and accumulation of IGF I mRNA. These inhibitory effects on *FSH* responses suggest that there could be a balance between protein kinase A and protein kinase C pathways in regulating differentiation in pig granulosa cells.

5/3,AB/39
DIALOG(R)File 155:MEDLINE(R)

08560318 95317445 PMID: 7796929
Growth hormone releasing factor and vasoactive intestinal peptide stimulate rat granulosa cell plasminogen activator activity in vitro during follicular development.
Karakji E G; Tsang B K
Department of Obstetrics and Gynaecology, University of Ottawa, Ontario, Canada.
Molecular and cellular endocrinology (IRELAND) Jan 1995, 107 (1) p105-12, ISSN 0303-7207 Journal Code: 7500844
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Growth hormone-releasing factor (GRF) and vasoactive intestinal peptide (VIP) are two structurally homologous peptides sharing common target cell receptor and known to enhance *FSH*-*induced* steroidogenesis of undifferentiated granulosa cell in vitro. Although VIP, has been reported to stimulate plasminogen activator (PA) activity in rat granulosa cells, our knowledge on the actions and interactions of these two peptides with *FSH* in the regulation of rat granulosa cell PA system during follicular development remains incomplete. Undifferentiated and differentiated rat granulosa cells from pre-antral (DES-treated rats) and antral (eCG-treated rats) follicles, respectively, were cultured in a chemically defined medium in the absence and presence of *FSH* (400 ng/ml), GRF (10(-8)-10(-5) M) and/or VIP (10(-9)-10(-5) M). Net secreted (PAs) and cell-associated (PAc) PA activities was measured by the fibrinolysis assay and characterized by the fibrin overlay method. Granulosa cell differentiative (progestin secretion) and proliferative (DNA synthesis) responses were analyzed by radioimmunoassay and [3H]thymidine incorporation, respectively. Both GRF and VIP stimulated PAs and PAc activities in a concentration-dependent manner in 24-h cultures of granulosa cells from the two stages of follicular development. They (10(-5) M) enhanced *FSH*-stimulated PAs activity in granulosa cell cultures of pre-antral follicles, with GRF being more effective than VIP. On the contrary, only GRF (10 microM) potentiated *FSH*-*induced* PAs and PAc activities

in cultures of granulosa cell from antral follicles. The stimulation of PA activity by these agonists decreased with the duration of culture irrespective of the stage of follicular development.(ABSTRACT TRUNCATED AT 250 WORDS)

5/3,AB/40
DIALOG(R)File 155:MEDLINE(R)

08378562 95140022 PMID: 7838150
Antisense epidermal growth factor oligodeoxynucleotides inhibit follicle-stimulating hormone-*induced* in vitro DNA and progesterone synthesis in hamster preantral follicles.
Roy S K; Harris S G
Leland J. and Dorothy H. Olson Center for Women's Health, Department of Obstetrics and Gynecology, University of Nebraska Medical Center, Omaha 68198-4515.
Molecular endocrinology (Baltimore, Md.) (UNITED STATES) Sep 1994, 8 (9) p1175-81, ISSN 0888-8809 Journal Code: 8801431
Contract/Grant No.: HD-18165; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Whether *FSH*-*induced* follicular DNA synthesis in the hamster involves epidermal growth factor (EGF) message *induction* and translation was evaluated using antisense EGF oligodeoxynucleotides. The 15 base pair antisense oligomers synthesized according to mouse EGF cDNA sequence downstream from the 5'-ATG start site hybridized with a 4.4-kilobase message of mouse submaxillary glands and with 4.0 kilobases of mRNA of hamster submaxillary glands, kidney, and ovaries. Preantral follicles at stages 1-7 were enzymatically and mechanically isolated from adult, cyclic hamsters on day 4:0900 h (day 1 = estrus), and follicles at stages 1-5 were isolated from hamsters hypophysectomized for 10 days. Follicles were preexposed to either antisense or sense EGF thio-oligomers for 1, 12, or 24 h and then cultured for an additional 24 h in the absence or presence of ovine-*FSH* (100 ng/ml) or recombinant murine EGF (50 ng/ml), and 1 microCi/ml [3H]thymidine. Follicular [3H]thymidine incorporation and EGF and steroid (progesterone, androstenedione, and 17 beta-estradiol) production were monitored to assess the molecular mechanism of *FSH* regulation of follicular development. Antisense oligomers significantly inhibited *FSH*-*induced* follicular DNA synthesis and progesterone but not androgen or estrogen production with a latency of 24 h. The oligomer inhibition of *FSH* action was effectively reversed by exogenous EGF. Antisense oligomers significantly inhibited follicular EGF synthesis in vitro. These results suggest that EGF message is expressed in the hamster ovary, and one of the molecular mechanisms of *FSH* regulation of hamster preantral folliculogenesis involves EGF mRNA *induction* and translation.(ABSTRACT TRUNCATED AT 250 WORDS)

5/3,AB/41
DIALOG(R)File 155:MEDLINE(R)

08343352 95100713 PMID: 7802429
[Intragonadal regulation of human follicular genesis: facts and hypotheses]
Regulation intragonadique de la folliculogenese humaine: faits et hypotheses.
Gougeon A
INSERM U-355, Clamart.
Annales d'endocrinologie (FRANCE) 1994, 55 (2) p63-73, ISSN 0003-4266 Journal Code: 0116744
Document type: Congresses; Review; Review, Academic ; English Abstract Languages: FRENCH
Main Citation Owner: NLM
Record type: Completed
In the mammalian ovary, the follicular growth is classically considered to be under the control of pituitary gonadotropins. In the human, three cycles (85 days) are required for a preantral follicle (approximately 0.15 mm in diameter) to attain the ovulatory size (approximately 20 mm in diameter). During this growing phase, follicular responsiveness to LH and especially to *FSH* exhibits strong changes. Up to diameter of approximately 2mm, follicles are unsensitive to cyclic changes in circulating levels of *FSH* , in terms of quality, growth rate and steroidogenesis (basal follicular growth). Follicles larger than 2 mm become responsive to *FSH*, in terms of quality and growth rate, but their ability to synthesize estrogen remains very low, they constitute the population of recruitable follicles. From its selection, the follicle destined to ovulate becomes mores and more responsive, first to *FSH* and then to LH; all the gonadotropin-*induced* functions are expressed during preovulatory maturation. The aim of this review is to clarify the intraovarian regulations involved: (a) in the inhibition of gonadotropin- *induced* functions (basal follicular growth); (b) in the acceleration of the growth rate of recruitable follicles and simultaneous acquisition of *FSH* responsiveness of their granulosa cells during the late luteal phase, as well as in the "selection" of one of them; (c) in the strong proliferation of granulosa cells paralleling with full *expression* of *FSH*-*induced* functions (preovulatory maturation before LH surge) and (d) in the inhibition of granulosa cell proliferation paralleling with full *expression* of *FSH*- and LH-*induced* functions (preovulatory maturation after the LH surge). Some peptides and proteins, such as growth factors (EGF, IGFs et IGFBPs, TGF-beta), the inhibin-activin-follistatin system and TNF-alpha, and synthesized by the follicular tissues, might be involved in both the inhibition and stimulation of follicular responsiveness to gonadotropins. Their possible role during maturation of the primate follicle has been analyzed in the light of the most recent findings.

5/3,AB/42
DIALOG(R)File 155:MEDLINE(R)

08304659 95064097 PMID: 7973806
The inhibitory effect and its mechanism of transferrin on *FSH*- *induced* differentiation of granulosa cells]
Yu J H; Guo J; Guo J; Zeng F X; Tang G H
Department of Reproductive Physiology, Sichuan Family Planning Research Institute, WHO Collaborating Center for Research in Human Reproduction, Chengdu.
Sheng li xue bao Acta physiologica Sinica (CHINA) Jun 1994, 46 (3) p209-16, ISSN 0371-0874 Journal Code: 20730130R
Document type: Journal Article; Review; Review, Tutorial ; English Abstract
Languages: CHINESE
Main Citation Owner: NLM
Record type: Completed
Transferrins are a class of related metal-binding transport

glycoproteins for transporting iron to various organs and tissues of the body. In recent years, it has been reported that the transferrin can play an important role in the local regulation of ovarian function, apart from its iron-binding characteristic. Transferrin could attenuate *FSH*-*induced* differentiation of rat and human granulosa cells and its mechanisms were considered as follows: (1) Transferrins partially blocked the binding of *FSH* with its receptors on granulosa cells and reduced the formation of intracellular cAMP, and therefore inhibited the *expression* of *FSH* receptors. (2) Acting sites beyond cAMP formation also existed for the inhibitory effect of transferrin on inhibin and estradiol production. (3) The inhibitory effect of transferrin seemed not to be involved in the changes of protein kinase C activity, the calcium release and "proliferation-differentiation reversed mechanism" in granulosa cells.

5/3,AB/43
DIALOG(R)File 155:MEDLINE(R)

08295244 95053519 PMID: 7964286
Human growth hormone augmentation of epidermal growth factor binding sites on rat granulosa cells.
Hattori M A; Shinohara Y; Yoshino E; Kanzaki M; Kojima I; Horiuchi R Institute of Endocrinology, Gunma University, Japan.
Journal of endocrinology (ENGLAND) Jul 1994, 142 (1) p69-75, ISSN 0022-0795 Journal Code: 0375363
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The effect of human GH (hGH) on the regulation of epidermal growth factor (EGF) receptor was investigated during differentiation of *FSH*-treated rat granulosa cells, which has been reported to be mediated by a cAMP-dependent mechanism. By measuring the binding of [125I]iodo-EGF to the intact cells, *FSH* was shown to cause increases in the number of EGF binding sites after culture for 72 h. When granulosa cells were cultured with hGH, the number of *FSH*-*induced* EGF binding sites was augmented, with a half-maximal effect at about 10 micrograms hGH/l and a maximal stimulatory concentration of 100 micrograms/l. The stimulatory effect of hGH was absolutely dependent on insulin which by itself showed stimulatory effects on EGF binding sites. Scatchard analysis of EGF binding sites indicated that treatment with hGH increased the number of EGF binding sites (17,200 sites/cell after treatment with *FSH*; 31,700 sites/cell after *FSH* plus hGH), but did not alter the binding affinity. The augmentation was observed after culturing for 48 h and increased progressively with time, reaching 280% of the level after *FSH* treatment by 120 h. Although progesterone synthesis was increased by hGH, the markers of cell differentiation such as cAMP synthesis and LH binding sites were suppressed, indicating hGH inhibition of the cAMP-mediated signal. The action of hGH on the EGF binding sites was not accompanied by cell proliferation. These findings indicate that hGH has a novel action on the regulation of rat granulosa cell EGF binding sites and that the granulosa cell may possess both cAMP-dependent and -independent mechanisms for *expression* of EGF binding sites.

5/3,AB/44
DIALOG(R)File 155:MEDLINE(R)

08243557 95003958 PMID: 7920181
Comparative IL-6 effects on *FSH* and hCG-*induced* functions in porcine granulosa cell cultures.
Machelon V; Nome F; Salesse R
Institut National de la Sante et de la Recherche Medicale (INSERM), Unit 355 Maturation Gametique et Fecondation, Clamart, France.
Cellular and molecular biology (Noisy-le-Grand, France) (FRANCE) May 1994, 40 (3) p373-80, ISSN 0145-5680 Journal Code: 9216789 Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Gonadotropin regulation of granulosa cell (GC) differentiation can be modulated by non-steroidal factors, including cytokines. Interleukin-6 (IL-6), a broad spectrum cytokine, has been previously demonstrated to be produced by GCs and to directly influence follicle stimulating hormone (*FSH*) differentiated functions of ovarian GCs. In the present study, primary cultures of GCs were prepared from prepubertal sow ovaries. No significant amount of biological active IL-6 was detected in these cultures using the B9 cell growth bioassay. Although our findings suggest that GCs are not source of IL-6 in the porcine ovary, this cytokine may be released by leukocytes present in the ovary and modulate ovarian functions by acting on GCs. Here, adding recombinant human (rh)IL-6 to GC cultures inhibited differentiated functions *induced* by *FSH* such as aromatase activity, LH receptor (LHr) *expression* measured by specific 125I-hCG binding and progesterone (P) production. On the opposite, rhIL-6 did not modulate stimulatory human chorionic hormone (hCG) effects on P release by GCs and did not prevent hCG binding to LHr. These preliminary results clearly showed that IL-6 acted differently on *FSH* and hCG *induced* functions although these gonadotropins act primarily through the same transduction pathway involving generation of cyclic AMP. We suggest that IL-6 might act more likely by reducing *FSH* binding capacity than by modulating transduction pathways. Inhibitory IL-6 effects on *FSH*-*induced* functions were not neutralized by adding to culture media a monoclonal antibody against the human IL-6 signal transducer gp130, previously reported to inhibit IL-6 mediated effects in human cell lines.

5/3,AB/45
DIALOG(R)File 155:MEDLINE(R)

08185228 94321877 PMID: 8046308
Functional *expression* of the recombinant human *FSH* receptor. Minegishi T; Igarashi S; Nakamura K; Nakamura M; Tano M; Shinozaki H; Miyamoto K; Ibuki Y
Department of Obstetrics and Gynecology, Gunma University School of Medicine, Japan.
Journal of endocrinology (ENGLAND) May 1994, 141 (2) p369-75, ISSN 0022-0795 Journal Code: 0375363
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The functional capacity of the recombinant human *FSH* (hFSH) receptor was tested on the basis of gonadotrophin stimulation of cyclic AMP (cAMP) production by transient transfections of 293 cells and stable transfections of Chinese hamster ovary (CHO) cells. A CHO cell line expressed with the

hFSH receptor cDNA covering the entire amino acid coding region revealed the presence of *FSH* binding site (Kd 6.2 x 10(-10) M) on the plasma membrane. Treatment of transfected cells with hFSH *induced* dose-dependent increases in intracellular cAMP production. These results indicate that the hFSH receptor functionally couples with endogenous adenylyl cyclase. Although rat *FSH* also *induced* dose-dependent increases in cAMP production, bovine *FSH* was effective only at high doses and human chorionic gonadotropin did not alter cAMP levels compared with control values. Northern blot analysis with a cRNA probe derived from hFSH receptor cDNA indicated the presence of two common *FSH* receptor mRNA transcripts (2.4 and 4.1 kb) in RNA prepared from a human ovary and transfected cell lines. Preincubation of CHO cells expressing a functional hFSH receptor (CHO-FSHR) with *FSH* for 16 h decreased the subsequent cAMP production resulting from a 30-min pulse of *FSH* stimulation. These results indicate that desensitization of the adenylyl cyclase response to *FSH* stimulation occurs in CHO-FSHR cells. This cell line therefore provides a tool with which to pursue detailed studies on the molecular basis of *FSH*-*induced* desensitization.

5/3,AB/46
DIALOG(R)File 155:MEDLINE(R)

08123612 94252232 PMID: 7514996
Tyrosine kinase inhibitor AG18 arrests follicle-stimulating hormone- *induced* granulosa cell differentiation: use of reverse transcriptase-polymerase chain reaction assay for multiple messenger ribonucleic acids.
Orly J; Rei Z; Greenberg N M; Richards J S
Department of Cell Biology, Baylor College of Medicine, Houston, Texas 77030.
Endocrinology (UNITED STATES) Jun 1994, 134 (6) p2336-46, ISSN 0013-7227 Journal Code: 0375040
Contract/Grant No.: HD-16229; HD; NICHD; HD-16272; HD; NICHD Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A sensitive assay of multiple mRNAs by reverse transcriptase-polymerase chain reaction was adopted to study the hormonally regulated *expression* of steroidogenic enzymes in primary rat granulosa cells in culture. As little as 15-60 ng total RNA prepared from cultured cells were reverse transcribed in the presence of pd(T)6, and polymerase chain reaction was conducted in the presence of specific oligonucleotide pairs designed to identify cDNAs of steroidogenic enzymes. In combination with Northern blot analysis of cholesterol side-chain cleavage cytochrome P450 (P450scc) message, it is shown that a novel protein kinase inhibitor, tyrphostin AG18, arrests the *FSH*-*induced* accumulation of P450scc mRNA. This inhibition is dose dependent (IC50, 15 microM) and reversible. The addition of 80 microM AG18 to cells containing high levels of P450scc mRNA caused a rapid decline of the cytochrome message (t 1/2, 5 h), similar to the effect of 30 micrograms/ml alpha-amanitin. However, concomitant addition of the two drugs did not accelerate the mRNA degradation process, suggesting that AG18 does not affect message stabilization. Tyrphostin AG18 did not affect mRNA species that are not *FSH* inducible, such as the ribosomal protein L19, or the constitutively expressed low levels of steroid 5 alpha-reductase mRNA. Moreover, even the extremely high levels of P450scc mRNA in granulosa-lutein cells, being cAMP independent and terminally differentiated a few hours after LH surge, were not affected by the addition of AG18 in culture. In contrast, two additional key and *FSH* -inducible steroidogenic enzymes, i.e. aromatase cytochrome P450 and 3 beta-hydroxysteroid dehydrogenase-I, were inhibited by AG18 at their mRNA levels. These results suggest that an as yet undetermined tyrosine kinase pathway is involved in the cAMP-dependent signal transduction pathway of *FSH* action, so that the presence of AG18 does not allow *FSH* *induction* of gene *expression* to occur.

5/3,AB/47
DIALOG(R)File 155:MEDLINE(R)

08123611 94252231 PMID: 8194459
Effect of activin on luteinizing hormone-human chorionic gonadotropin receptor messenger ribonucleic acid in granulosa cells.
Nakamura K; Nakamura M; Igarashi S; Miyamoto K; Eto Y; Ibuki Y; Minegishi T
Department of Obstetrics and Gynecology, Gunma University School of Medicine, Japan.
Endocrinology (UNITED STATES) Jun 1994, 134 (6) p2329-35, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Activin (the dimer of inhibin beta-subunit) is involved in the modulation of granulosa cell function. Recent reports have indicated that activin had an effect on LH/human CG (hCG) receptor *induction* and steroidogenesis in granulosa cells. To characterize the regulation inducing LH/hCG receptor by activin, we investigated messenger RNA (mRNA) levels, the *expression* of the LH/hCG receptor, and intracellular cAMP accumulation in cultured rat granulosa cells. Northern blot analysis showed an increase in the LH/hCG receptor mRNA level with *FSH* (30 ng/ml) and activin (100 ng/ml) cotreatment, whereas activin alone could not augment LH/hCG receptor mRNA at all. After the addition of actinomycin D to the culture medium, LH/hCG receptor mRNA was more stable in the presence of *FSH* plus activin than in the presence of *FSH* alone. Similarly, a receptor binding assay revealed that the cotreatment with *FSH* and activin *induced* more LH/hCG receptor than *FSH* alone 96 h after exposure to hormone, but that activin (100 ng/ml) alone could not induce the LH/hCG receptor. Since the primary, if not the sole, second messenger mediating the action of *FSH* in granulosa cells has been shown to be cAMP, intracellular cAMP accumulation was measured in granulosa cells in the presence of *FSH* (30 ng/ml) and/or activin (100 ng/ml). Although *FSH* -stimulated cAMP accumulation reached a peak 15 min after incubation, activin did not significantly alter cAMP accumulation in either control nor *FSH* -stimulated granulosa cells, indicating that the effects of activin on the LH/hCG receptor in granulosa cells are not mediated by the increase in cAMP. These results demonstrate that activin enhances the *FSH*-*induced* LH/hCG receptor mRNA, LH/hCG receptor mRNA stability, and LH/hCG binding sites not due to the stimulation of the adenylate cyclase system. Although the signal pathway from the activin receptor has not been elucidated upon yet, activin is capable of increasing LH/hCG receptor levels

through the accumulation of LH/hCG receptor mRNA levels.

5/3,AB/48
DIALOG(R)File 155:MEDLINE(R)

08074035 94221371 PMID: 8167918
Rat Sertoli cell aromatase cytochrome P450: regulation by cell culture conditions and relationship to the state of cell differentiation. Papadopoulos V; Jia M C; Culty M; Hall P F; Dym M
Department of Cell Biology, Georgetown University Medical Center, Washington, D.C. 20007.
In vitro cellular & developmental biology. Animal (UNITED STATES) Dec 1993, 29A (12) p943-9, ISSN 1071-2690 Journal Code: 9418515 Contract/Grant No.: HD16260; HD; NICHD; HD24633; HD; NICHD Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Primary cultures of immature rat Sertoli cells in plastic dishes are highly responsive to follicle stimulating hormone (*FSH*) and its second messenger, cAMP, in metabolizing testosterone to estradiol, thus indicating the presence of an active, hormone-regulated aromatase cytochrome P450 (P450arom). However, in vivo studies indicated that P450arom is *FSH* -responsive only in very young animals, where the cells have not yet differentiated, but they lose this ability later on in development. Sertoli cells grown on Matrigel (a reconstituted basement membrane), laminin (a basement membrane component), or in bicameral chambers coated with Matrigel, assume structural and functional characteristics more similar to that of in vivo differentiated Sertoli cells. When the cells were cultured on laminin or Matrigel, the *FSH*- and cAMP-*induced* estradiol production was greatly reduced by 30 and 60%, respectively. When Sertoli cells were cultured in bicameral chambers coated with Matrigel, no *induction* of testosterone aromatization by *FSH* or cAMP was observed. However, *FSH*-*induced* cAMP formation was greater when the cells were cultured on basement membrane or in the chambers than on plastic dishes. These results suggest that culture conditions favoring the assumption by Sertoli cells of a phenotype closer that of the differentiated cells in vivo (tall columnar and highly polarized) suppress the *induction* of P450arom by *FSH* and cAMP. We then examined the mechanism(s) by which cell phenotype affects p450arom activity. Northern blot analyses of Sertoli cell RNA revealed one major band of 1.9 Kb and two minor bands of 3.3 and 5.2 Kb. However, there were no changes at the level of the *expression* of P450arom messenger RNA under the different culture conditions.(ABSTRACT TRUNCATED AT 250 WORDS)

5/3,AB/49
DIALOG(R)File 155:MEDLINE(R)

08051003 94176558 PMID: 8130275
Granulosa cell luteinizing hormone receptor *expression* is modulated by ganglioside-specific ligands.
Hattori M; Kanzaki M; Kojima I; Horiuchi R
Institute of Endocrinology, Gunma University, Japan.
Biochimica et biophysica acta (NETHERLANDS) Mar 10 1994, 1221 (1) p47-53, ISSN 0006-3002 Journal Code: 0217513
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The ganglioside GM1 (Gal beta 1-->3GalNAc beta 1-->4[NeuAc alpha 2-->3] Gal beta 1-->4Glc beta 1-->1Cer) was synthesized during granulosa cell development in vitro, and the effect of the interaction between cell-surface GM1 and its ligands on the luteinizing hormone (LH) receptor *expression* was investigated. GM1 synthesis, demonstrated by metabolic labeling of glycosphingolipids with [3H]galactose and binding studies using the 125I-B-subunit of cholera toxin, a specific ligand for GM1, was increased in follicle-stimulating hormone (*FSH*)-treated granulosa cells. When granulosa cells were cultured for 72 h in a medium containing the B-subunit of cholera toxin, *FSH*-*induced* LH-receptor contents determined by measuring the binding of 125I-deglycosylated human chorionic gonadotropin to intact cells, was augmented. The stimulatory effect of the B-subunit was dependent on the *FSH* concentration and culture duration. The augmentation was observed after culture for 48 h, and marked increases were evident after 72 h, which coincided with an increase of the 125I-B-subunit binding capacity. Scatchard analysis of the LH-receptor binding indicated that treatment with the B-subunit increased the number of LH-binding sites (6580 sites/cell after treatment with 20 ng/ml *FSH*; 11,290 sites/cell after *FSH* plus 100 ng/ml B-subunit), but did not alter the binding affinity. A specific antibody against GM1 mimicked the stimulatory effect of the B-subunit. The augmentation was not accompanied by granulosa cell proliferation. These findings suggest that binding of exogenous or possible endogenous ligands to cell-surface GM1 produces signals and modulates the cellular behavior during granulosa cell development.

5/3,AB/50
DIALOG(R)File 155:MEDLINE(R)

07741710 93274662 PMID: 1304034
Luteinizing hormone pulses, follicle-stimulating hormone and control of follicle selection in sheep.
McNeilly A S; Crow W; Brooks J; Evans G
MRC Reproductive Bioloy Unit, University of Edinburgh, UK.
Journal of reproduction and fertility. Supplement (ENGLAND) 1992, 45 p5-19, ISSN 0449-3087 Journal Code: 0225652
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The growth of large oestrogenic follicles that have the potential to ovulate if given an appropriate luteinizing hormone (LH) signal is dictated by the plasma concentration of follicle-stimulating hormone (*FSH*). Basal amounts of LH are essential for this *FSH*-*induced* follicle growth, but pulses of LH do not appear to be essential. The fall in *FSH* concentration during the follicular phase of the oestrous cycle in sheep, and the subsequent withdrawal of *FSH* from other developing follicles may not be sufficient to explain follicle selection. There is little evidence to support an active suppression of the growth of other follicles by a factor(s) produced by the dominant, or selected follicle. It is possible that LH pulses cause active atresia of non-selected follicles. The selected follicle is the one that can survive the fall in plasma *FSH* and the large increase in LH pulses during the follicular phase and selection may simply be a case of being the follicle(s) that is present at the correct time to receive adequate *FSH*

and develop sufficiently to survive the inhibitory effects of LH pulses. Several mechanisms whereby LH pulses may inhibit follicle growth are suggested, and avenues for future research, particularly related to the *expression* of the LH receptor on granulosa cells of the developing follicle, are outlined.

5/3,AB/51
DIALOG(R)File 155:MEDLINE(R)

07632550 93145890 PMID: 8381074
The promoter of the gene encoding 3',5'-cyclic adenosine monophosphate (cAMP) response element binding protein contains cAMP response elements: evidence for positive autoregulation of gene transcription. Meyer T E; Waeber G; Lin J; Beckmann W; Habener J F
Laboratory of Molecular Endocrinology, Massachusetts General Hospital, Boston 02114.
Endocrinology (UNITED STATES) Feb 1993, 132 (2) p770-80, ISSN 0013-7227 Journal Code: 0375040
Contract/Grant No.: DK-25532; DK; NIDDK; DK-30457; DK; NIDDK Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The transcriptional transactivational activities of the phosphoprotein cAMP-response element-binding protein (CREB) are activated by the cAMP-dependent protein kinase A signaling pathway. Dimers of CREB bind to the palindromic DNA element 5'-TGACGTCA-3' (or similar motifs) called cAMP-responsive enhancers (CREs) found in the control regions of many genes, and activate transcription in response to phosphorylation of CREB by protein kinase A. Earlier we reported on the cyclical *expression* of the CREB gene in the Sertoli cells of the rat testis that occurred concomitant with the *FSH*-*induced* rise in cellular cAMP levels and suggested that transcription of the CREB gene may be autoregulated by cAMP-dependent transcriptional proteins. We now report the structure of the 5'-flanking sequence of the human CREB gene containing promoter activity. The promoter has a high content of guanosines and cytosines and lacks canonical TATA and CCAAT boxes typically found in the promoters of genes in eukaryotes. Notably, the promoter contains three CREs and transcriptional activities of a promoter-luciferase reporter plasmid transfected to placental JEG-3 cells are increased 3- to 5-fold over basal activities in response to either cAMP or 12-O-tetradecanoyl phorbol-14-acetate, and give 6- to 7-fold responses when both agents are added. The CREs bind recombinant CREB and endogenous CREB or CREB-like proteins contained in placental JEG-3 cells and also confer cAMP-inducible transcriptional activation to a heterologous minimal promoter. Our studies suggest that the *expression* of the CREB gene is positively autoregulated in trans.

5/3,AB/52
DIALOG(R)File 155:MEDLINE(R)

07611694 93121946 PMID: 8380382
Tyrphostins inhibit follicle-stimulating hormone-mediated functions in cultured rat ovarian granulosa cells.
Gomberg-Malool S; Ziv R; Re'em Y; Posner I; Levitzki A; Orly J
Department of Biological Chemistry, Alexander Silberman Institute of Life Sciences, Hebrew University of Jerusalem, Israel.
Endocrinology (UNITED STATES) Jan 1993, 132 (1) p362-70, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
FSH *induces* the *expression* of cholesterol side-chain cleavage cytochrome P450 (P450scc) in rat ovarian granulosa cells. The present study reveals that the tyrphostin AG18, a member of novel protein tyrosine kinase inhibitors, can arrest the *FSH*-*induced* synthesis of P450scc with an apparent IC50 of 30 microM. Total inhibition of P450scc *expression* was achieved at 80 microM AG18. AG18-mediated inhibition of P450scc was also observed when the enzyme was *induced* by prostaglandin E2, forskolin, or 8-bromo-cAMP. Studies examining functional LH receptors showed that the tyrphostin inhibits the *expression* of *FSH*-*induced* LH receptors. The drug did not affect *FSH*-*induced* cAMP accumulation, suggesting that it may interfere with the flow of *FSH* signal transduction at a site distal intracellular accumulation of cAMP. Control experiments demonstrated that the inhibitory action of AG18 was reversible, did not hamper total protein synthesis in the cells, and did not change the adenine nucleotide (ATP:ADP:AMP) ratio or their levels in the treated cells. A cell-free assay of cAMP-dependent protein kinase showed that the tyrphostin AG18 does not affect this enzyme activity up to concentrations above 200 microM. These results suggest that a putative tyrosine kinase activity is involved in the gonadotropin signal transduction pathway leading to *expression* of functional genes in ovarian cells.

5/3,AB/53
DIALOG(R)File 155:MEDLINE(R)

07588625 93109310 PMID: 8380222
Transcriptional regulation of the rat tissue type plasminogen activator gene: localization of DNA elements and nuclear factors mediating constitutive and cyclic AMP-*induced* *expression*. Ohlsson M; Leonardsson G; Jia X C; Feng P; Ny T
Department of Applied Cell and Molecular Biology, University of Umea, Sweden.
Molecular and cellular biology (UNITED STATES) Jan 1993, 13 (1) p266-75, ISSN 0270-7306 Journal Code: 8109087
Contract/Grant No.: HD-12303; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have characterized tissue type plasminogen activator (tPA) promoter elements and nuclear factors required for follicle-stimulating hormone (*FSH*)-*induced* transcription of the rat tPA gene in granulosa cells and constitutive *expression* of the gene in the rat neuroblastoma cell line B103. Run-on transcription analysis of isolated nuclei revealed that B103 cells transcribe the tPA gene at a high and constitutive level, while *FSH* was found to induce tPA gene transcription in a rapid and transient manner in granulosa cells. The maximal *FSH*-*induced* transcription rate was obtained after 20 min and was similar in the absence or presence of the protein synthesis inhibitor cycloheximide. However, in the presence of cycloheximide, tPA transcription was not turned off but continued at a high rate for several hours. This phenomenon may at least partly explain the earlier finding that tPA mRNA is superinduced by *FSH* in the presence of

cycloheximide. DNase I footprinting analysis of the first 621 bp of the tPA promoter revealed a total of six regions that interact with nuclear factors from B103 and granulosa cells. Deletion of the promoter region from positions -269 to -621, a region that includes the two most-upstream footprints, had no effect on constitutive or *FSH*-*induced* transcription in transient *expression* experiments. Nuclear extracts from both granulosa cells and B103 cells showed strong binding to a consensus cyclic AMP-responsive element (CRE) at positions -178 to -185 and a neighboring binding site for nuclear factor 1 (NF1) at positions -145 to -158. The factors binding to these two regions were identified as members of the CRE-binding protein and NF1 families of transcription factors, respectively. Footprints were also obtained over two GC boxes at positions -64 to -71 and -41 to -49. These footprints were more pronounced with nuclear extracts from B103 cells than with extracts from untreated or *FSH* -treated granulosa cells, but gel shift assays indicate that similar amounts of two distinct factors bind to the two GC boxes in both cell types. Transfection experiments using promoter constructs with inactivated promoter elements indicate that both the CRE and NF1 sites contribute to the *FSH* responsiveness of the rat tPA gene in granulosa cells, while only the NF1 site is important for constitutive *expression* in B103 cells. The two GC boxes were found to be necessary both for constitutive *expression* in B103 cells and for *FSH*- *induced* *expression* in granulosa cells, and inactivation of both GC boxes essentially eliminated the tPA promoter activity in both cell types.

5/3,AB/54
DIALOG(R)File 155:MEDLINE(R)

07550355 93076727 PMID: 1446630
Basic fibroblast growth factor (bFGF) gene *expression* and protein production during pubertal development of the seminiferous tubule: follicle-stimulating hormone-*induced* Sertoli cell bFGF *expression*.
Mullaney B P; Skinner M K
Reproductive Endocrinology Center, University of California, San Francisco 94143-0556.
Endocrinology (UNITED STATES) Dec 1992, 131 (6) p2928-34, ISSN 0013-7227 Journal Code: 0375040
Contract/Grant No.: HD-20583; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The potential role of basic fibroblast growth factor (bFGF) as a mediator of cell-cell interactions in the growth and development of the testis was examined. Nuclease protection analysis was used to evaluate bFGF gene *expression* in the testis and other male reproductive tract tissues. bFGF *expression* was evident in seminal vesicle, prostate, epididymis, and, at low levels, testis of 20-day-old rats. The developmental *expression* of bFGF in whole testis and isolated somatic cells types was determined. Mesenchymal-derived peritubular cells and epithelial-like Sertoli cells were isolated from prepubertal, midpubertal, and late pubertal rat testes. In whole testis, bFGF *expression* is predominant early in prepubertal testicular development and decreases with sexual maturity. Both freshly isolated peritubular and Sertoli cells express bFGF at relatively constant levels during pubertal development, with a slight suppression at the late pubertal stages. Freshly isolated mature Leydig cells also expressed low levels of bFGF. Cultured Sertoli and peritubular cells produced bFGF-like proteins, including 18- and 24-kilodalton forms. Interestingly, *FSH* increased Sertoli cell bFGF gene *expression* and protein production. Previously, *FSH* and bFGF have been shown to stimulate immature Sertoli cell growth. The results of the current study suggest that the ability of *FSH* to regulate testis and Sertoli cell proliferation may in part be indirectly mediated through the local production and action of bFGF. bFGF has also previously been shown to localize in developing germinal cells. Therefore, *FSH*-*induced* Sertoli cell bFGF *expression* may mediate Sertoli-germinal cell interactions involved in the control of the spermatogenic process. Observations demonstrate the presence of bFGF at a time coinciding with active growth of the somatic cell populations of the seminiferous tubule. Potential roles for bFGF in the seminiferous tubule to consider include angiogenesis of the tubule, prepubertal Sertoli cell proliferation, and mediating Sertoli-germinal cell interactions.

5/3,AB/55
DIALOG(R)File 155:MEDLINE(R)

07495732 93024484 PMID: 1328874
Follicle-stimulating hormone increases guanine nucleotide-binding regulatory protein subunit alpha i-3 mRNA but decreases alpha i-1 and alpha i-2 mRNA in Sertoli cells.
Loganzo F; Fletcher P W
Department of Biochemistry and Molecular Biology Albany Medical College, New York 12208.
Molecular endocrinology (Baltimore, Md.) (UNITED STATES) Aug 1992, 6 (8) p1259-67, ISSN 0888-8809 Journal Code: 8801431
Contract/Grant No.: S07RR05394; RR; NCRR
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
FSH interacts with a guanine nucleotide-binding protein (G-protein)-coupled receptor, which in turn modulates signal transduction via the G-protein subunit alpha s. However, it is unknown whether *FSH* regulates alpha-subunit gene *expression* and whether G-protein alpha-subunit genes other than alpha s are modulated in *FSH* -stimulated signal transduction. Regulation of mRNA for alpha s and alpha i-2 was studied in primary cultures of rat Sertoli cells because these proteins are linked to the control of adenylyl cyclase. In addition, mRNA for alpha i-1 and alpha i-3 were quantified because these proteins are putatively linked to ion channels but have not been well characterized in the Sertoli cell. Northern blot analyses demonstrated that *FSH* *induced* a dose-dependent increase in steady state levels of alpha i-3 mRNA. In contrast, *FSH* caused a dose-dependent decrease in levels of alpha i-1 and alpha i-2 mRNA. No significant effect of *FSH* on alpha s mRNA levels was detectable. The time course of *FSH* effects showed a 75% decrease in alpha i-1 mRNA levels, a 50% decrease in alpha i-2 mRNA levels and a nearly 3-fold increase in levels of alpha i-3 mRNA between 4-6 h of treatment with 100 ng/ml *FSH*. Steady state levels of alpha i-1 and alpha i-2 mRNA returned to pretreatment levels after 10 h *FSH* treatment, while alpha i-3 mRNA returned to a new steady state level approximately 50% greater than the pretreatment level.(ABSTRACT TRUNCATED AT 250 WORDS)

5/3,AB/56
DIALOG(R)File 155:MEDLINE(R)

07477592 93003892 PMID: 1327204
Regulation of cyclic adenosine 3',5'-monophosphate-dependent protein kinase activity and regulatory subunit RII beta content by basic fibroblast growth factor (bFGF) during granulosa cell differentiation: possible implication of protein kinase C in bFGF action.
Oury F; Faucher C; Rives I; Bensaid M; Bouche G; Darbon J M
INSERM U133, Faculte de Medecine Rangueil, Toulouse, France.
Biology of reproduction (UNITED STATES) Aug 1992, 47 (2) p202-12, ISSN 0006-3363 Journal Code: 0207224
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have previously shown that basic fibroblast growth factor (bFGF) inhibits the *FSH*-*induced* differentiation of cultured rat granulosa cells, as manifested by prominent reduction of the LH receptor *expression* . We now investigate the possible sites and mechanism of action of bFGF. Whereas bFGF decreased the cAMP formation *induced* by *FSH* , it enhanced the cAMP production caused by cholera toxin and forskolin, suggesting that bFGF exerted its inhibitory action on cell differentiation at a step to cAMP production. Photoaffinity labeling with 8-azido-[32P]cAMP revealed that bFGF markedly reduced the *FSH*- *induced* increase in the level of regulatory subunit RII beta of the cAMP-dependent protein kinase (PKA) type II. In contrast to its striking effect on RII beta *expression* (70-80% inhibition), bFGF decreased PKA enzymatic activity by only 30%. On the other hand, transforming growth factor-beta (TGF beta) slightly amplified the stimulatory action of *FSH* and antagonized the bFGF inhibitory effect on both LH receptor *expression* and RII beta synthesis. We report that the protein kinase C (PKC) activator 12-O-tetradecanoylphorbol-13-acetate (TPA), which impaired granulosa cell differentiation, also abolished the RII beta synthesis *induced* by *FSH* . The activation of PKC by bFGF in granulosa cells was supported by the following findings: (i) bFGF markedly enhanced the production of diacylglycerol (2.3-fold stimulation at 5 min), the intracellular activator of PKC; (ii) bFGF promoted tight association of PKC to cellular membranes, a process that is believed to correlate with the enzyme activation; (iii) bFGF *induced* the phosphorylation of an endogenous M(r) 78,000/pI 4.7 protein that appears as a specific PKC substrate; (iv) bFGF mimicked the TPA-*induced* transmodulation of the epidermal growth factor (EGF) receptor, reducing by 36% the 125I-EGF binding on granulosa cells. We conclude that bFGF may exert its repressive action on RII beta synthesis, PKA activity, and granulosa cell differentiation by primarily targeting PKC activation.

5/3,AB/57
DIALOG(R)File 155:MEDLINE(R)

07472869 92410773 PMID: 1326831
Increase in the *expression* of thyroid hormone receptors in porcine granulosa cells early in follicular maturation.
Maruo T; Hiramatsu S; Otani T; Hayashi M; Mochizuki M
Department of Obstetrics and Gynecology, Kobe University School of Medicine, Japan.
Acta endocrinologica (DENMARK) Aug 1992, 127 (2) p152-60, ISSN 0001-5598 Journal Code: 0370312
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Thyroid hormone has been demonstrated to synergize with *FSH* to exert stimulatory effects on the differentiation of porcine granulosa cells. In order to further characterize the nature of thyroid hormone action on granulosa cells, the presence of triiodothyronine (T3) receptors in the nuclei of porcine granulosa cells was examined, and qualitatively and quantitatively compared during follicular maturation. Then, comparative abilities of granulosa cells from varying follicle stages to respond to T3 were assessed in terms of *FSH*-*induced* LH/hCG receptor formation and progesterone secretion. Furthermore, the *expression* of erb-A was analyzed using Northern blot hybridization of porcine granulosa cell RNA with a v-erb-A probe. Binding experiments with [125I]T3 showed that granulosa cell nuclei obtained from small follicles had a greater ability to bind [125I]T3 compared to those from large follicles. Scatchard analysis revealed the presence of nuclear T3 receptors with a single class of binding sites. There was little difference in the affinity of the T3 receptors during follicular maturation. By contrast, the number of the T3 receptors was higher in small follicle granulosa cells compared to that in large follicle granulosa cells. Thus, the increased T3 binding to small follicle granulosa cells relative to large follicle granulosa cells appears to be attributable to the increased number of the nuclear T3 receptors rather than to a change in the affinity. The magnitude of the stimulatory effects of T3 on granulosa cell functions was maximal in small follicle granulosa cells, but negligible in large follicle granulosa cells.(ABSTRACT TRUNCATED AT 250 WORDS)

5/3,AB/58
DIALOG(R)File 155:MEDLINE(R)

07435602 92371333 PMID: 1324158
Transient down-regulation of androgen receptor messenger ribonucleic acid (mRNA) *expression* in Sertoli cells by follicle-stimulating hormone is followed by up-regulation of androgen receptor mRNA and protein. Blok L J; Hoogerbrugge J W; Themmen A P; Baarends W M; Post M; Grootegoed J A
Department of Endocrinology and Reproduction, Medical Faculty, Erasmus University, Rotterdam, The Netherlands.
Endocrinology (UNITED STATES) Sep 1992, 131 (3) p1343-9, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Cooperative actions of *FSH* and androgens on initiation, maintenance, and restoration of spermatogenesis have been described. In the present experiments the regulatory effects of *FSH* on androgen receptor (AR) gene *expression* in Sertoli cells were studied. In immature rats injection of *FSH* (1 microgram/g BW, ip) resulted in a rapid down-regulation of testicular AR mRNA *expression* (4 h), followed by recovery to the control level (10 h). Using cultured immature Sertoli cells, a similar transient effect on AR mRNA *expression* was observed after the addition of *FSH* (500 ng/ml) or (Bu)2cAMP (0.5 mM). Cycloheximide treatment of the cells did not prevent the rapid

FSH- *induced* down-regulation of AR mRNA *expression*, indicating that de novo protein synthesis is not required for this effect. Furthermore, using a transcriptional run-on assay, no marked decrease in the rate of AR gene transcription was found upon treatment of the cultured Sertoli cells with *FSH* for 2 or 4 h. This demonstrates that the short term effect of *FSH* or AR mRNA *expression* reflects a change in mRNA stability. The AR protein level was not markedly affected by the transient decrease in AR mRNA *expression* . When immature Sertoli cells were incubated with *FSH* for longer time periods (24-72 h), both AR mRNA and protein *expression* were increased. In Sertoli cells isolated from 15-day-old rats, this increase was higher (mRNA, 2- to 3-fold; protein, 2-fold) than in Sertoli cells isolated from 25-day-old animals. The results indicate that *FSH* plays a complex role in the regulation of AR *expression* in immature rat Sertoli cells.

5/3,AB/59
DIALOG(R)File 155:MEDLINE(R)

07340687 92273624 PMID: 1591267
Follistatin inhibits activin-*induced* differentiation of rat follicular granulosa cells in vitro.
Nakamura T; Hasegawa Y; Sugino K; Kogawa K; Titani K; Sugino H
Frontier Research Program, Institute of Physical and Chemical Research (RIKEN), Wako, Japan.
Biochimica et biophysica acta (NETHERLANDS) Apr 30 1992, 1135 (1) p103-9, ISSN 0006-3002 Journal Code: 0217513
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The effect of follistatin on activin-*induced* granulosa cell differentiation was investigated in freshly harvested granulosa cells from diethylstilbestrol (DES)-treated rats. Activin *induced* a remarkable change in granulosa cellular morphology from elongated fibroblast-like to round cells, which follistatin prevented. Follistatin itself had no influence on the cellular morphology. We studied the action of follistatin on activin-*induced* differentiation of granulosa cells cultured in a chemically defined medium. Addition of activin (30 ng/ml) to the culture increased the *FSH* binding site approximately 2-fold compared with the control (spontaneous *expression*) level, whereas follistatin reduced the activin-*induced* *expression* level to the control level in a concentration-dependent manner. Activin (30 ng/ml) markedly augmented *FSH*-*induced* hCG binding and progesterone production by approximately 20-fold, and these effects were suppressed by follistatin in a concentration-dependent manner. Similarly, addition of follistatin to the culture *induced* a concentration-dependent decrease of activin-enhanced inhibin-producing activity, but had no effect on *FSH* -*induced* inhibin production. These results suggest that follistatin/activin-binding protein binds to activin stoichiometrically to suppress the activin-*induced* differentiation of rat granulosa cell in vitro, but follistatin itself has no direct effect on activin-independent reactions.

5/3,AB/60
DIALOG(R)File 155:MEDLINE(R)

07240136 92184003 PMID: 1665832
Tumor-promoting phorbol ester acts synergistically with insulin to induce lutropin receptor *expression* in rat granulosa cells.
Hattori M; Takahashi M; Horiuchi R
Department of Pharmaceutical Chemistry, Gunma University, Maebashi, Japan.
Molecular and cellular endocrinology (NETHERLANDS) Oct 1991, 81 (1-3) p69-76, ISSN 0303-7207 Journal Code: 7500844
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Lutropin (LH) receptors in rat granulosa cells are expressed by activation of cAMP-dependent protein kinase in response to follitropin (*FSH*). In the present study, 12-O-tetradecanoylphorbol 13-acetate (TPA) could cause a dose-dependent *expression* of LH receptors in the presence of insulin, but not in the absence of insulin, as measured by binding of 125I-deglycosylated human choriogonadotropin (DGhCG). The synergistic action of TPA with insulin was achieved at 1 nM and 10 mIU/ml, respectively. The receptor *expression* *induced* by this synergistic action was accompanied by cAMP accumulation which was detected after a lag time of 6 h following exposure to TPA. However, a synthetic diacylglycerol and non-protein kinase C activating phorbol derivatives did not mimic the effect of TPA on the receptor *expression*. In addition, insulin modulated the inhibitory effect of TPA in *FSH*-*induced* LH receptor *expression*, indicating a peculiar action of insulin in the receptor *expression* . Indomethacin treatment led to a dose-dependent inhibition in the receptor *expression* in the cells treated with TPA plus insulin more than that in the cells with *FSH* plus insulin, suggesting that the synergistic action was dependent upon cyclooxygenase and/or phospholipase A2 activity. It was shown by Scatchard analysis of LH receptors and kinetic studies of hCG-stimulated cAMP formation that the synergistic action of TPA with insulin led to *expression* of functional LH receptors coupled with the adenylate cyclase system in cultured granulosa cells.

5/3,AB/61
DIALOG(R)File 155:MEDLINE(R)

07203709 92137480 PMID: 1723386
Follitropin receptor down-regulation involves a cAMP-dependent post-transcriptional decrease of receptor mRNA *expression*.
Themmen A P; Blok L J; Post M; Baarends W M; Hoogerbrugge J W; Parmentier M; Vassart G; Grootegoed J A
Department of Endocrinology and Reproduction, Medical Faculty, Erasmus University Rotterdam, The Netherlands.
Molecular and cellular endocrinology (NETHERLANDS) Jul 1991, 78 (3) pR7-13, ISSN 0303-7207 Journal Code: 7500844
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The regulation by *FSH* (follitropin; follicle-stimulating hormone) of *FSH* receptor mRNA and protein (*FSH* binding) was studied using cultured Sertoli cells isolated from 21-day-old rats. *FSH* *induced* a dose-dependent and almost complete down-regulation of receptor mRNA at 4 h after addition of the hormone. At subsequent time points (16 h and later) the *FSH* receptor mRNA levels had returned close to control values. The effect of *FSH* was mimicked by dibutyryl

cyclic AMP (dbcAMP) and forskolin, and the phosphodiesterase inhibitor methyl-isobutylxanthine (MIX) prolonged the *FSH* action. These findings indicate that the effect of *FSH* on its receptor mRNA was mediated by cAMP. A down-regulatory effect of *FSH* and dbcAMP on *FSH* receptor mRNA was also observed in the presence of the protein synthesis inhibitor cycloheximide, suggesting a direct effect of *FSH* /dbcAMP on the *expression* of the *FSH* receptor gene. Transcriptional run-on experiments revealed that *FSH* did not inhibit initiation of the *FSH* receptor gene; hence a post-transcriptional mechanism is involved. Binding of 125I-*FSH* to the cultured Sertoli cells was rapidly (4 h) decreased when the cells were incubated with *FSH* or *FSH* in combination with MIX. This effect can be explained by ligand-*induced* receptor sequestration. In contrast, incubation of Sertoli cells with dbcAMP had no effect on binding of 125I-*FSH* after 4 h, but resulted in a 60% loss of *FSH* binding sites after 24 h, probably caused by decreased mRNA *expression* . In conclusion, *FSH* receptor down-regulation in Sertoli cells is effected not only by the well-documented ligand-*induced* loss of receptors from the plasma membrane, but also involves a cAMP-mediated decrease of *FSH* receptor mRNA through a post-transcriptional mechanism.

5/3,AB/62
DIALOG(R)File 155:MEDLINE(R)

07130281 92064128 PMID: 1659543
Follicle-stimulating hormone increases c-fos mRNA levels in rat granulosa cells via a protein kinase C-dependent mechanism.
Pennybacker M; Herman B
Department of Cell Biology and Anatomy, University of North Carolina, Chapel Hill 27599.
Molecular and cellular endocrinology (NETHERLANDS) Sep 1991, 80 (1-3) p11-20, ISSN 0303-7207 Journal Code: 7500844
Contract/Grant No.: 2-P01-CA29589; CA; NCI; AG07218; AG; NIA; AG10104; AG ; NIA
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Recent evidence has been presented that follicle-stimulating hormone (*FSH*) stimulates the *induction* of granulosa cell c-fos protooncogene mRNA in vivo (Pennybacker and Herman (1989) J. Cell Biol. 109, 151A; Delidow et al. (1990) Endocrinology 126, 2302-2306), yet the mechanisms by which *FSH* *induces* c-fos mRNA *expression* have not been delineated. To elucidate the mechanisms of *FSH* -dependent c-fos mRNA *expression* , we measured the time and dose dependence of c-fos mRNA levels using Northern blot analysis in intact ovaries and cultured granulosa cells in response to *FSH*. In intact ovaries, *FSH*-*induced* c-fos mRNA *expression* was time dependent with maximal *expression* at 90 min post *FSH* injection, while in cultures of granulosa cells obtained from estrogen-primed immature female rats, c-fos mRNA levels were highest after 30 min exposure to *FSH* and at a concentration of 100 ng/ml. Neither 8-bromo adenosine 3',5'-cyclic monophosphate (8-br-cAMP), at doses ranging from 0.1 to 10 mM, nor 100 microM forskolin (in the presence or absence of 200 microM isobutyl-methylxanthine) or luteinizing hormone (LH, 100 ng/ml) were able to mimic *FSH*-*induced* c-fos mRNA *expression* in granulosa cell cultures. However, tetradecanoyl-13-phorbol acetate (TPA, 200 nM) was able to induce c-fos mRNA *expression*. The protein kinase C (PKC) inhibitors H-7 (0.3-30 microM) and staurosporine (0.75 micrograms/ml) blocked *FSH*-*induced* c-fos mRNA *expression* in cultured granulosa cells while HA 1004, an inhibitor of cGMP- and cAMP-dependent protein kinases at 30 microM had no effect on TPA-*induced* c-fos *expression*, and only minimally inhibited *FSH*-*induced* c-fos *expression*. Both *FSH* (100 ng/ml) and forskolin (3 microM) increased progesterone production in cultured granulosa cells. These data support the hypothesis that *FSH* specifically *induces* c-fos mRNA *expression* by a PKC-dependent mechanism and that the cAMP arm of the *FSH* response pathway is operant in these cells.

5/3,AB/63
DIALOG(R)File 155:MEDLINE(R)

06516105 90212607 PMID: 2108722
A synthetic peptide corresponding to human *FSH* beta-subunit 33-53 binds to *FSH* receptor, stimulates basal estradiol biosynthesis, and is a partial antagonist of *FSH*.
Coloma T A; Dattatreyamurty B; Reichert L E
Department of Biochemistry, Albany Medical College, New York 12208. Biochemistry (UNITED STATES) Feb 6 1990, 29 (5) p1194-200, ISSN 0006-2960 Journal Code: 0370623
Contract/Grant No.: HD-21388; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have previously shown that hFSH-beta 34-37 (KTCT) and 49-52 (TRDL) inhibit binding of 125I-hFSH to *FSH* receptor in calf testis membranes and that hFSH-beta 33-53, which encompasses these tetrapeptides, inhibits binding with increased potency. hFSH-beta 33-53 rapidly dimerizes under conditions utilized in the receptor binding assay (pH 7.5) so that the binding inhibition reported earlier was due to the hFSH-beta 33-53 dimer rather than the monomer. At pH 6.5, conversion to dimer does not occur, and binding inhibition could be unequivocally attributed to the monomer. Radioiodinated and alkylated hFSH-beta 33-53 binds to the *FSH* receptor with a Kd = (5.5 +/- 1.4) X 10(-5) M. The biological activity of hFSH-beta 33-53 was assessed by its ability to affect the conversion of androstenedione to estradiol in rat Sertoli cells cultures. *FSH*-beta 33-53 behaved as a partial antagonist of the *FSH*-*induced* estradiol synthesis. The required incubation medium, however, contains cystine as well as cystine, which rapidly forms a hFSH-beta Cys-(51)-S-S-Cys derivative at the pH of the incubation, 7.4. When hFSH-beta 33-53 was converted either to the hFSH-beta Cys(51)-S-S-Cys or to a carboxymethylated derivative, inhibition of *FSH*-*induced* estradiol synthesis still was observed. This result demonstrates that the free R-SH group at Cys51 is not responsible for the inhibition. *FSH* -beta 33-53 also significantly stimulated basal levels of estradiol synthesis, but not to maximal levels observed with *FSH* (partial agonist). Neither the carbohydrate content of hFSH-beta nor the alpha subunit of *FSH* appears to be essential for signal transduction and *expression* of the hormone effect of *FSH*-beta 33-53.

5/3,AB/64
DIALOG(R)File 155:MEDLINE(R)

06307331 89391956 PMID: 2551266

Tumor necrosis factor-alpha inhibits follicle-stimulating hormone- *induced* differentiation in cultured rat granulosa cells.
Darbon J M; Oury F; Laredo J; Bayard F
INSERM U168, Department of Endocrinology, CHU Rangueil, Universite Paul Sabatier, Toulouse, France.
Biochemical and biophysical research communications (UNITED STATES) Sep 15 1989, 163 (2) p1038-46, ISSN 0006-291X Journal Code: 0372516 Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have investigated the effects of TNF-alpha on *FSH*-*induced* LH receptor *expression*, cAMP and progesterone production in cultured rat granulosa cells. TNF-alpha (0.5-100 ng/ml) inhibits the stimulating action of *FSH* on LH receptor formation in a dose-dependent manner with an IC50 of 1 ng/ml and an almost complete suppression of LH receptor *induction* for 50-100 ng/ml TNF-alpha. The inhibitory effect of TNF-alpha is not due to variations in cell number or viability but rather to a reduction of the LH receptor content per cell with no change in binding affinity (KD = 0.8 x 10(-10)M). TNF-alpha also inhibits the *FSH*-*induced* cAMP production but at a lower extent, with a maximum reduction of 60% for 100 ng/ml TNF-alpha. Moreover, TNF-alpha impairs the LH receptor formation *induced* by forskolin, cholera toxin or 8-Bromo-cAMP, indicating that the cytokine also acts at a step distal to *FSH* receptor and to cAMP formation. Finally, TNF-alpha decreases dramatically the progesterone synthesis that is stimulated by *FSH*, with a reduction to undetectable levels on and after 10 ng/ml TNF-alpha. These results suggest that TNF-alpha may drastically reduce the capacity of granulosa cells to differentiate upon *FSH* stimulation and to respond to LH during the physiological ovarian follicular maturation. Such anti-gonadotropic action of TNF-alpha on granulosa cell differentiation may be also relevant to the alteration of ovarian function during physiopathological processes like inflammatory or infection diseases.

5/3,AB/65
DIALOG(R)File 155:MEDLINE(R)

06087084 89170472 PMID: 2494036
Developmental changes in luteinizing hormone/human chorionic gonadotropin steroidogenic responsiveness in marmoset granulosa cells: effects of follicle-stimulating hormone and androgens.
Shaw H J; Hillier S G; Hodges J K
Institute of Zoology, Zoological Society of London, United Kingdom. Endocrinology (UNITED STATES) Apr 1989, 124 (4) p1669-77, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Factors regulating LH/hCG responsiveness in primate granulosa cells were examined in the marmoset monkey (Callithrix jacchus). Granulosa cells were isolated and pooled from small antral (0.5-1.0 mm) and large preovulatory (greater than or equal to 2 mm) follicles from mid- to late follicular phase ovaries of cyclic marmosets. The cells from small and large follicles were cultured in serum-free medium for 48 h in the absence or presence of increasing concentrations of hCG (0.1-100 ng/ml) with or without 0.1 microM androgen [testosterone or 5 alpha-dihydrotestosterone (DHT)]. Granulosa cells from small follicles were also cultured in the absence or presence of a constant concentration of human *FSH* (30 ng/ml) with or without androgen for 48 h before exposure to hCG for an additional 48 h. Steroidogenic responsiveness was assessed by measuring progesterone accumulation in culture medium and aromatase activity in washed monolayers. Granulosa cells from large follicles showed dose-dependent increases in both progesterone accumulation and aromatase activity in response to treatment with hCG. In contrast, granulosa cells from small follicles were unresponsive to hCG. However, pretreatment of granulosa cells from small follicles for 48 h with *FSH* stimulated hCG responsiveness. The effects of both testosterone and DHT on hCG-stimulated aromatase activity and progesterone accumulation by granulosa cells from large preovulatory follicles were inhibitory. Testosterone and DHT also suppressed basal (no hCG) progesterone accumulation in these cells, but had no effect on basal aromatase activity. The effects of androgens on *FSH*-*induced* hCG responsiveness in immature granulosa cells were variable. The results show a development-related increase in marmoset granulosa cell responsiveness to LH/hCG and provide evidence that *FSH* and androgens interact to regulate the onset and *expression* of this critical event during preovulatory follicular development in the primate ovary.

5/3,AB/66
DIALOG(R)File 155:MEDLINE(R)

05963295 89050085 PMID: 2847713
Fibroblast growth factor regulates the *expression* of luteinizing hormone receptors in cultured rat granulosa cells.
Oury F; Darbon J M
Inserm U 168, Department of Endocrinology, CHU Rangueil, Universite Paul Sabatier, Toulouse, France.
Biochemical and biophysical research communications (UNITED STATES) Oct 31 1988, 156 (2) p634-43, ISSN 0006-291X Journal Code: 0372516 Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have investigated the effects of bFGF on both the *FSH*- *induced* LH receptor *expression* and cAMP production in cultured rat granulosa cells. Concentrations of pure FGF, from 10(-12) M to 10(-10) M, progressively inhibit the stimulatory actions of *FSH* with an ED50 of approximately 4 x 10(-12) M for both parameters. Higher FGF concentrations, from 4 x 10(-10) M to 10(-8) M, lead to a gradual reduction of the growth factor inhibitory effect. The effects of FGF are more prominent on the modulation of LH receptors than on the *FSH*- *induced* cAMP production. Moreover, FGF impairs the LH receptor formation *induced* by cholera toxin or 8-Bromo-cAMP, indicating that the growth factor also acts at a step distal to cAMP formation. The inhibitory effect of FGF on LH receptor *expression* increases during the entire course of granulosa cell differentiation, from 24 to 96 h, and is not due to variations in cell number or viability, but rather to a change in the content of LH receptors with no significant modification of binding affinity (KD congruent to 0.8 x 10(-10) M). These results suggest that bFGF may acutely regulate the capacity of granulosa cells to differentiate upon *FSH* stimulation and to respond to LH during the ovarian follicular maturation.

5/3,AB/67
DIALOG(R)File 155:MEDLINE(R)

05625267 88051123 PMID: 3118982
In vitro regulation of pig Sertoli cell growth and function: effects of fibroblast growth factor and somatomedin-C.
Jaillard C; Chatelain P G; Saez J M
INSERM U 307, Hopital Debrousse, Lyon, France.
Biology of reproduction (UNITED STATES) Oct 1987, 37 (3) p665-74, ISSN 0006-3363 Journal Code: 0207224
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The effects of insulin, somatomedin-C (Sm-C), epidermal growth factor (EGF), fibroblast growth factor (FGF), vitamin E, and retinoic acid on growth and function of immature cultured pig Sertoli cells were investigated. All these factors, except vitamin E, stimulated Sertoli cell DNA synthesis and proliferation. The mitogenic effects of insulin observed only at micromolar concentrations were similar to those *induced* by nanomolar concentrations of Sm-C or EGF, but significantly less than those *induced* by FGF. The effects of EGF and Sm-C were almost additive, whereas those of Sm-C and FGF were synergistic. After a 6-day treatment, FGF and retinoic acid *induced* a significant increase in the number of follicle-stimulating hormone (*FSH*) receptors per cell, and in *FSH*-*induced* cyclic adenosine 3',5'-monophosphate (cAMP) production. Sm-C, which alone had no effect on these two parameters, potentiated FGF action. Basal plasminogen activator activity was enhanced after the 6-day treatment with EGF plus insulin and, particularly, with FGF plus insulin. Similarly, the response of the latter group to *FSH* was significantly higher than in any other group of cells. FGF was also able to stimulate cell multiplication and enhanced the *FSH* receptor number of Sertoli cells isolated from 15- and 26-day-old rats. Thus, FGF is the most potent known mitogenic factor for cultured Sertoli cells, and it stimulates the phenotypic *expression* of these cells.

5/3,AB/68
DIALOG(R)File 155:MEDLINE(R)

05415490 87165979 PMID: 3104332
In vitro regulation of granulosa cell differentiation. Involvement of cytoskeletal protein *expression*.
Ben-Ze'ev A; Amsterdam A
Journal of biological chemistry (UNITED STATES) Apr 15 1987, 262 (11) p5366-76, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The link between the biochemical and morphological differentiation of granulosa cells was studied by investigating the organization and the *expression* of cytoskeletal proteins which determine cell shape and contacts. In cells treated with follicle-stimulating hormone (*FSH*), in a serum- and growth factor-free medium, or with other compounds which elevate cellular cAMP levels, the synthesis of the adherens junction proteins, vinculin, alpha-actinin, and actin was reduced significantly when compared to unstimulated cells (7-fold for vinculin, 5-fold for alpha-actinin, and 3-fold for actin). The in vitro translatability of the mRNAs coding for these proteins and the level of actin mRNA determined by RNA blot hybridization were generally reduced in differentiating cells. The synthesis and the organization of vimentin and tubulin was unaffected during this process, whereas the organization of actin and vinculin was dramatically affected, with *FSH*-treated cells displaying a diffuse pattern of actin and vinculin, with very little vinculin in adhesion plaques. Gonadotropin-releasing hormone agonist and the phorbol ester 12-O-tetradecanoylphorbol-13-acetate which are known to antagonize the cAMP-mediated biochemical differentiation of granulosa cells by reducing cAMP levels or by activating protein kinase C and phospholipid turnover, blocked to a large extent the *FSH*-*induced* effect on the adherens junction proteins. Epidermal growth factor, which blocked the *FSH*-*induced* cAMP increase, but not the *FSH*-*induced* progesterone production, failed to block the synthesis of vinculin, alpha-actinin, and actin. Cytochalasin B could induce steroidogenesis and similar changes in the synthesis of these cytoskeletal proteins, whereas fibronectin, which causes cell spreading, blocked in part the *FSH*- *induced* effect on the *expression* of cytoskeletal proteins. The modulation of cytoskeletal proteins may therefore be an essential feature of programmed differentiation events leading to the final phenotype of granulosa cells.

5/3,AB/69
DIALOG(R)File 155:MEDLINE(R)

05411753 87161570 PMID: 3030692
Bifunctional role of transforming growth factor-beta during granulosa cell development.
Knecht M; Feng P; Catt K
Endocrinology (UNITED STATES) Apr 1987, 120 (4) p1243-9, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Regulatory actions of transforming growth factor-beta (TGF beta) on granulosa cell function were analyzed in cells cultured from the ovaries of diethylstilbestrol-implanted rats. In the presence of a suboptimal concentration of *FSH* (5 ng/ml) that increased LH receptors by 100-fold during a 72-h culture, TGF beta augmented this response in a dose-dependent manner with a maximal effect at 16 pM. In contrast, the growth factor inhibited the LH receptor response to an optimal dose of *FSH* (50 ng) by up to 50% and was inactive in the absence of gonadotropin. TGF beta also enhanced the formation of cAMP by 5 ng *FSH* and partially inhibited the effects of higher *FSH* concentrations. However, the actions of TGF beta were more prominent on LH receptor *induction* than on cAMP production with either low or high amounts of *FSH*. In addition, TGF beta had little effect on cAMP production stimulated by cholera toxin or forskolin, but amplified the actions of these ligands as well as that of 8-bromo-cAMP on LH receptor *expression*. TGF beta also modulated the steroidogenic activity of the granulosa cells, with increased production of progesterone in response to 5-100 ng *FSH*. The bifunctional actions of TGF beta on *FSH*- *induced* LH receptor formation were observed throughout a 96-h culture period. However, the presence of the growth factor was not required for the first 24 h of culture, indicating that TGF beta alters the later events

involved in LH receptor formation. TGF beta augmented the stimulatory actions of 5 ng *FSH* on LH receptors in the absence or presence of insulin, but its inhibitory effect on these receptors was only observed in cells treated with insulin. These results indicate that TGF beta modifies *FSH* action during granulosa cell development in a biphasic manner. TGF beta can exert stimulatory or inhibitory effects depending upon the concentration of *FSH* and the presence of insulin, and these are due to alterations in cAMP action as well as cAMP production. Autocrine and/or endocrine actions of TGF beta during granulosa cell differentiation may be involved in the processes of follicle selection and development.

5/3,AB/70
DIALOG(R)File 155:MEDLINE(R)

05285912 87033603 PMID: 3095315
Transforming growth factor beta regulates the inhibitory actions of epidermal growth factor during granulosa cell differentiation. Feng P; Catt K J; Knecht M
Journal of biological chemistry (UNITED STATES) Oct 25 1986, 261 (30) p14167-70, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The effects of transforming growth factor beta (TGF-beta) on epidermal growth factor (EGF) receptor content and EGF action were studied in cultured granulosa cells from immature diethylstilbestrol-implanted rats. During follicle-stimulating hormone (*FSH*)-*induced* differentiation in vitro, EGF receptors increased by 20-fold as measured by the binding of 125I-EGF to the intact cells. Addition of TGF-beta during the 48-h culture period amplified the stimulatory effects of *FSH* on EGF receptors up to 2-fold, with ED50 and maximal concentrations of 2.5 and 8 pM, respectively. Also TGF-beta alone in amounts from 1.6 to 16 pM increased EGF receptor content 4-fold. The stimulatory effects of TGF-beta were due to increased numbers of EGF receptors/cell, since the growth factor had no effect on the Kd (3-5 X 10(-11) M) of the high-affinity EGF binding site. TGF-beta action was observed within 20 h of granulosa cell culture and was maximal by 48 h of a 96-h culture. The stimulatory actions of TGF-beta in gonadotropin-*induced* cells were exerted through the cAMP effector system of the granulosa cell, since the growth factor also amplified the *induction* of EGF receptors by cholera toxin, forskolin, and 8-bromo-cAMP. The augmentation of EGF receptors by TGF-beta resulted in a parallel 2-fold increase in the inhibitory effects of EGF on *FSH*- *induced* cAMP production and luteinizing hormone receptor *expression* during granulosa cell development. TGF-beta did not increase granulosa cell numbers during culture although it elevated [3H]thymidine incorporation into DNA by 2-fold over that of *FSH* -treated cells. These results indicate that TGF-beta regulates the effects of both *FSH* and EGF during granulosa cell differentiation and provides evidence that ovarian function may be controlled by the combined actions of gonadotropins and multiple growth factors.

5/3,AB/71
DIALOG(R)File 155:MEDLINE(R)

05031640 86094256 PMID: 3001707
Inhibition of gonadotropin-*induced* granulosa cell differentiation by activation of protein kinase C.
Shinohara O; Knecht M; Catt K J
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Dec 1985, 82 (24) p8518-22, ISSN 0027-8424 Journal Code: 7505876
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The *induction* of granulosa cell differentiation by follicle-stimulating hormone (*FSH*) is characterized by cellular aggregation, *expression* of luteinizing hormone (LH) receptors, and biosynthesis of steroidogenic enzymes. These actions of *FSH* are mediated by activation of adenylate cyclase and cAMP-dependent protein kinase and can be mimicked by choleragen, forskolin, and cAMP analogs. Gonadotropin releasing hormone (GnRH) agonists inhibit these maturation responses in a calcium-dependent manner and promote phosphoinositide turnover. The phorbol ester phorbol 12-myristate 13-acetate (PMA) also prevented *FSH*-*induced* cell aggregation and suppressed cAMP formation, LH receptor *expression*, and progesterone production, with an ID50 of 0.2 nM. In *FSH*-treated cells, PMA did not reduce the initial increase in cAMP formation during the first 24 hr of culture but prevented its secondary increase from 24 to 48 hr. PMA also inhibited LH receptor *induction* by cholera toxin, forskolin, and 8-bromo-cAMP, but it did not impair cAMP responses to the former two agents, indicating that the site of action of the phorbol ester is distal to adenylate cyclase. The early stimulation of cAMP-dependent protein kinase activity by *FSH* was also unaffected by PMA, consistent with its lack of effect on the initial cAMP response to *FSH*. However, PMA caused a marked decrease in cytosolic protein kinase C activity within 1 min of its addition to the cells. The permeant diacylglycerols, 1-oleoyl-2-acetoyl-sn-glycerol and sn-1,2-dioctanoyl glycerol, also inhibited LH receptor formation, while the nonpermeant diacylglycerol, diolein, was inactive. These results indicate that in situ activation of protein kinase C by PMA or permeant diacylglycerols inhibits cAMP-dependent granulosa cell differentiation, and suggest that the inhibitory actions of GnRH agonists on granulosa cell maturation are also mediated by protein kinase C.

5/3,AB/72
DIALOG(R)File 155:MEDLINE(R)

05027932 86109038 PMID: 3002876
[The biocellular effect of thyroid hormone on functional differentiation of porcine granulosa cells in culture]
Hayashi M; Maruo T; Matsuo H; Mochizuki M
Nippon Naibunpi Gakkai zasshi (JAPAN) Oct 20 1985, 61 (10) p1189-96, ISSN 0029-0661 Journal Code: 0413717
Document type: Journal Article ; English Abstract
Languages: JAPANESE
Main Citation Owner: NLM
Record type: Completed
To elucidate if the thyroid hormone acts directly on the ovary, the biocellular effect of L-thyroxine (T4) on porcine granulosa cells cultured in vitro was investigated. Monolayer cultures of porcine granulosa cells obtained from small (1 approximately 2 mm), medium (3 approximately 5 mm) or large (6

approximately 11 mm) follicles were carried out in the presence of porcine *FSH* (100 ng/ml). Concomitant treatment with T4 promoted *FSH* -dependent morphological luteinization, i.e. alteration of immature granulosa cells obtained from small follicles to epithelioid form. T4 also increased *FSH*-stimulated *induction* of hCG/LH receptor on immature granulosa cells. Furthermore, T4 augmented *FSH*-mediated production of progesterone and estradiol by immature granulosa cells cultured in vitro. The concentration of T4 to produce the maximal stimulatory effect was 10-7 M, demonstrating that optimal concentration of thyroid hormone is required for the *expression* of this stimulatory action. Since T4 alone demonstrated no effect on the differentiation of porcine granulosa cells and all the stimulatory effect of T4 seems to have a permissive action on *FSH*-*induced* granulosa cell luteinization. Although insulin showed a similar effect on porcine granulosa cells, no stimulation of estradiol production by porcine granulosa cells was observed with insulin in the culture system used in this study. These results suggest that the thyroid hormone acts directly on the ovary and plays an important role in modifying the *FSH*-dependent cellular differentiation of immature granulosa cells.

5/3,AB/73
DIALOG(R)File 155:MEDLINE(R)

04876078 85257194 PMID: 2990868
Aromatase inhibitors prevent granulosa cell differentiation: an obligatory role for estrogens in luteinizing hormone receptor *expression*.
Knecht M; Brodie A M; Catt K J
Endocrinology (UNITED STATES) Sep 1985, 117 (3) p1156-61, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
To determine the role of newly synthesized estrogens in LH receptor *expression* , granulosa cells from diethylstilbestrol-implanted immature rats were cultured with *FSH* plus aromatase inhibitors. When present throughout the 48-h culture period, 4-hydroxy-4-androstene-3,17-dio ne (4-OHA; greater than or equal to 100 microM) and 1,4,6-androstatriene-3,17-dione (greater than or equal to 5 microM) inhibited *FSH*-*induced* LH receptor formation by 40% and 90%, respectively. Both aromatase inhibitors caused relatively greater inhibition of LH receptor formation when added from 20-48 h of culture, the period during which *FSH* -stimulated estrogen synthesis occurs (85% maximal inhibition with 4-OHA and 95% with 1,4,6-androstatriene-3,17-dione) . Addition of estradiol, but not androstenedione, reversed the reduction of LH receptor formation by 4-OHA, indicating that the effects of the aromatase inhibitors were specifically related to their blockade of estradiol synthesis. The stimulation of estrogen production by *FSH* alone (8-fold) or with androstenedione (80-fold) during the 48-h culture period was prevented by 4-OHA. *FSH*-stimulated cAMP production was initially enhanced by 4-OHA from 0-20 h of culture, but was reduced from 20-48 h. Lower concentrations of 4-OHA (less than or equal to 50 microM) amplified *FSH* -stimulated cAMP production and LH receptor formation. However, these responses were blocked by the antiestrogen keoxifene or the antiandrogen flutamide, indicating that 4-OHA or a metabolite may have partial estrogenic or androgenic properties. The inhibitory effects of higher concentrations of 4-OHA on LH receptor *expression* were potentiated by keoxifene or flutamide. These results indicate that estrogen production and action are necessary for LH receptor *expression* in the granulosa cell.

5/3,AB/74
DIALOG(R)File 155:MEDLINE(R)

04790749 85179307 PMID: 2985371
Inhibition of hormone-*induced* steroidogenesis during cell proliferation in serum-free cultures of rat granulosa cells.
Epstein-Almog R; Orly J
Endocrinology (UNITED STATES) May 1985, 116 (5) p2103-12, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Long term cultures of rat granulosa cells were grown in serum-free medium, consisting of Dulbecco's modified Eagle's medium mixed 1:1 with Ham's nutrient F-12 medium and supplemented with insulin, transferrin, hydrocortisone, and fibronectin (4F medium). In sparse cultures (10(4) cells/cm2), the granulosa cells were steroidogenically responsive to ovine *FSH* (NIADDK-oFSH-15) during days 1-2 and 10-14 (responsive periods). The major steroids produced were 20 alpha-hydroxyprogesterone (20 alpha-OH-P) and 5 alpha-pregnane, 3 alpha,20 alpha-diol (pregnanediol). However, as of day 3, the cells gradually lost their steroidogenic responsiveness which was inhibited by 88% at day 7 (refractory period). Nevertheless, from day 8 onward, the cells regained their responsiveness which was fully restored at day 12. The transient loss of responsiveness was uniquely associated with progestin biosynthesis, since *FSH*- *induced* aromatase activity declined to background levels within 12 days and was never restored again. The loss of progestin responsiveness was not due to lack of cAMP because *FSH* *induced* increasing levels of cAMP accumulation, reaching maximal values on day 7 in culture. On the other hand, the onset of the refractory period occurred concomitantly with the entry of the cultured cells into a synchronous proliferation phase, during which the cell population doubled. Thereafter, as DNA synthesis ceased, the cells regained their steroidogenic responsiveness. A deliberate arrest of cell replication, in the presence of excess thymidine or in high density cultures, prevented the temporal loss of activity. The data presented favor the notion that cell proliferation and *expression* of differentiated functions are inversely related. It is suggested that growth-related processes suppress steroidogenesis by an as yet unknown mechanism.

5/3,AB/75
DIALOG(R)File 155:MEDLINE(R)

04543836 84232328 PMID: 6203565
Inhibitory actions of adenosine on follicle-stimulating hormone- *induced* differentiation of cultured rat granulosa cells. Knecht M; Darbon J M; Ranta T; Baukal A; Catt K J
Biology of reproduction (UNITED STATES) Jun 1984, 30 (5) p1082-90, ISSN 0006-3363 Journal Code: 0207224
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

To determine the effects of adenosine on follicle-stimulating hormone (*FSH*)-*induced* differentiation, granulosa cells isolated from the ovaries of diethylstilbestrol-treated immature rats were cultured with increasing concentrations of the nucleoside and modulators of adenosine action. Although adenosine had no effect on basal granulosa cell function during 48 h of culture, concentrations of the nucleoside from 10 microM to 1 mM progressively inhibited *FSH*-*induced* responses, including progesterone production and *expression* of *FSH* and luteinizing hormone (LH) receptors. Adenosine had biphasic effects on *FSH* -stimulated cAMP accumulation, causing inhibition of cAMP production at 10 to 100 microM and stimulation at higher concentrations. The enhancement of cAMP production by 1 mM adenosine occurred during the first 24 h of culture, while both 100 microM and 1 mM adenosine reduced *FSH* -stimulated cAMP production from 24 to 48 h. The inhibitory effects of adenosine were prevented by adenosine deaminase and dipyridamole, an inhibitor of adenosine transport, and were antagonized by 1-methyl-3-isobutylxanthine. The inhibition of cAMP and progesterone production by adenosine was partially overcome when cells were washed and reincubated with forskolin, but not with *FSH*. Adenine, guanosine, and inosine at concentrations of 100 microM did not modify *FSH*-*induced* cAMP formation or LH receptor *induction*. These results indicate that adenosine exerts predominantly inhibitory actions on hormone- *induced* granulosa cell differentiation, as manifested by prominent reductions in steroidogenesis and gonadotropin receptor *expression*.

5/3,AB/76
DIALOG(R)File 155:MEDLINE(R)

04350534 84032711 PMID: 6313708
Epidermal growth factor and gonadotropin-releasing hormone inhibit cyclic AMP-dependent luteinizing hormone receptor formation in ovarian granulosa cells.
Knecht M; Catt K
Journal of cellular biochemistry (UNITED STATES) 1983, 21 (3) p209-17, ISSN 0730-2312 Journal Code: 8205768
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The *induction* of luteinizing hormone (LH) receptors was studied in granulosa cells prepared from the ovaries of hypophysectomized diethylstilbestrol-treated immature rats. Incubation of granulosa cells for 48 h with increasing concentrations of follicle-stimulating hormone (*FSH*) or choleragen caused parallel rises in cAMP levels and LH receptors. These observations, with the finding that 8-Bromo-cAMP also *induced* LH receptor formation, indicate that hormonal stimulation of LH binding sites is mediated by cAMP. Peptide hormones that inhibited *FSH*-stimulated cAMP production, such as epidermal growth factor (EGF) and a gonadotropin-releasing hormone agonist (GnRHa), also prevented LH receptor formation. GnRHa and EGF had negligible effects on *FSH* -stimulated cAMP production from 0 to 24 h of culture, but reduced cAMP accumulation by 80% and 90%, respectively, from 24 to 48 h when the majority of LH receptors appeared. *FSH*-sensitive adenylate cyclase activity, as measured by the conversion of (3H)-ATP to (3H)-cAMP, was inhibited by GnRHa and EGF at 48 h of culture. EGF and GnRHa also reversed the inhibiton of ectophosphodiesterase activity caused by *FSH* in granulosa cells between 48 and 72 h of culture. Both EGF and GnRHa inhibited *induction* of LH receptors by 8-Bromo-cAMP, suggesting that their effects are also on cAMP action. Addition of GnRHa, but not EGF, between 36 and 48 h of culture completely prevented further increases in LH receptors *induced* by 8-Bromo-cAMP, indicating that the inhibitory action of GnRHa can be initiated at later times during granulosa cell differentiation, whereas full *expression* of EGF action requires a longer period. These results demonstrate that EGF and GnRH inhibit *FSH*-*induced* LH receptor formation in the granulosa cell by reducing hormone-dependent cAMP production and also by impairing the ability of cAMP to stimulate LH receptor formation.

5/3,AB/77
DIALOG(R)File 155:MEDLINE(R)

04268734 83261617 PMID: 6307657
The cAMP-Dependent *induction* of LH receptors in primary cultures of porcine granulosa cells is not due to the *expression* of an intracellular pool of LH receptors.
Segaloff D L; Limbird L E
Endocrinology (UNITED STATES) Aug 1983, 113 (2) p825-7, ISSN 0013-7227 Journal Code: 0375040
Contract/Grant No.: AM 06878; AM; NIADDK; HD 16027; HD; NICHD; RR 05424; RR; NCRR; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The present studies examined whether the increase in cell surface LH receptors in primary cultures of porcine granulosa cells after exposure to *FSH* or cholera toxin, agents that increase intracellular cAMP, is due to de novo synthesis of the receptor or to a cAMP-dependent translocation of an intracellular pool of LH receptors to the cell surface. LH receptor *induction* by *FSH* was fully inhibited by the addition of cycloheximide to the incubation media, but resumed after cycloheximide was removed. These data suggest that *FSH*-*induced* LH receptor appearance requires protein synthesis. However, to be confident that the inhibition of LH receptor appearance did not result from lack of transit of preformed receptors requiring a rapidly turning over pool of proteins, we assayed for possible latent receptors in the cell interior by extracting granulosa cells with Triton X-100. Under conditions which detected about 74% of LH receptors in cells exposed to cholera toxin, little [125]iodo-hCG-binding activity was detected in cells not exposed to a cAMP-promoting stimulus. These findings suggest that a preformed pool of LH receptors does not exist in untreated cells, and that the cAMP-mediated *induction* of LH receptors requires de novo synthesis of the receptor.

5/3,AB/78
DIALOG(R)File 155:MEDLINE(R)

03468458 81022642 PMID: 6774812
Serum suppresses the *expression* of hormonally *induced* functions in cultured granulosa cells.
Orly J; Sato G; Erickson G F
Cell (UNITED STATES) Jul 1980, 20 (3) p817-27, ISSN

0092-8674 Journal Code: 0413066
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Growth and function of primary cultures of granulosa cells obtained from immature, hypophysectomized, estrogen-treated rats were compared in serum-containing and serum-free media. In serum-free medium (1:1 mixture of DMEM:F-12) supplemented with insulin, hydrocortisone, transferrin and fibronectin (4F medium), the cells remained healthy and steroidogenically responsive for at least 60 days in culture. The growth profile of the granulosa cells in 4F medium was similar to that obtained in serum-containing medium. In both media cell proliferation did not exceed more than one cell doubling. DMEM:F-12 alone did not support the cell viability. Upon *FSH* stimulation, the cells produced 25 fold more progestin and estrogen per cell in 4F medium than in medium supplemented with 5% serum. This effect was not directly related to serum proteins which mediate cell adhesion since cells cultured in dishes precoated with serum remained steroidogenically responsive to *FSH* . Cholera toxin and Bt2-cAMP readily stimulated progestin production in the presence of serum. The inhibitory effect of serum was not reversed by adding the four factors to serum-containing medium. The factors were essential for the *FSH*- *induced* steroidogenesis in serum-free medium. After four days of incubation in 4F medium, the cells showed a transient loss of their ability to produce progestin in response to *FSH*. In both 4F medium as well as in serum-containing medium, the cells regained their hormonal responsiveness after 35 days in culture. Since the loss of hormonal responsiveness occurred at the same time as growth was initiated in the cultures, it is suggested that the *FSH*-*induced* steroidogenesis is negatively controlled by growth-related processes.

5/3,AB/79
DIALOG(R)File 155:MEDLINE(R)

03057993 79127188 PMID: 217610
Independence of steroidogenic capacity and luteinizing hormone receptor *induction* in developing granulosa cells.
Hillier S G; Zeleznik A J; Ross G T
Endocrinology (UNITED STATES) Mar 1978, 102 (3) p937-46, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The relationship between *FSH*-*induced* acquisition of LH/hCG receptors and the steroidogenic capacity of granulosa cells from estrogen-primed hypophysectomized rat ovaries has been examined. Granulosa cells harvested from the immature preantral follicles of animals not treated with *FSH* (controls) displayed negligible specific human [125I]iodo-hCG binding and produced only minimal amounts of progesterone during 48 h of culture in vitro. Addition of highly purified hFSH or prostaglandin-E2 (PGE2) to the culture medium elicited substantial increases in progesterone production which were not accompanied by measurable increases in [125I]iodo-hCG binding. Treatment with oFSH in vivo for 24 h led to the initiation of antrum formation in many follicles and was accompanied by an 8-10-fold increase in hCG binding by freshly isolated granulosa cells. Basal, hFSH-, and PGE2-stimulated progesterone production during culture was also greater than controls. In contrast, cells from animals receiving oFSH in vivo for only 12 h showed no increase in hCG binding either before or after culture, yet basal and stimulated progesterone production in vitro was significantly greater than controls, indicating that the initiation of steroidogenesis was antecedent to LH/hCG receptor *induction*. Only those cells obtained after the 24-h in vivo treatment with oFSH produced elevated amounts of progesterone when incubated in the presence of hCG, thereby showing that the observed increases in [125I]iodo-hCG binding reflected the *induction* of functionally active LH/hCG receptors. Pharmacological stimulation of steroidogenesis by cell suspensions with N,O'-dibutyryl cAMP resulted in consistently high levels of progesterone production irrespective of previous treatment with *FSH* in vivo. This uniform *expression* of in vitro steroidogenic capacity occurred in the complete absence of measurable increases in LH/hCG receptors, suggesting that these two fundamental developmental processes are independent phenomena which may be under separate regulation in vivo.

File 411:DIALINDEX(R)

DIALINDEX(R)
(c) 2002 The Dialog Corporation plc

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Items	File

>>>Invalid syntax
? s fsh()(induced or induces) adj2 expression

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s fsh()(induced or induces) adj2 expression

Items	File

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Items	File
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1	65: Inside Conferences_1993-2002/Dec W1
11	71: ELSEVIER BIOBASE_1994-2002/Dec W1
22	73: EMBASE_1974-2002/Nov W4
1	94: JICST-EPlus_1985-2002/Sep W5

1 98: General Sci Abs/Full-Text_1984-2002/Oct
1 143: Biol. & Agric. Index_1983-2002/Oct 8 144: Pascal_1973-2002/Dec W1
21 155: MEDLINE(R)_1966-2002/Nov W3
1 156: ToxFile_1965-2002/Nov W3
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8 399: CA SEARCH(R)_1967-2002/UD=13723

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N3	21	155: MEDLINE(R)_1966-2002/Nov W3
N4	18	34: SciSearch(R) Cited Ref Sci_1990-2002/Dec W1 N5
	11	71: ELSEVIER BIOBASE_1994-2002/Dec W1
N6	9	50: CAB Abstracts_1972-2002/Oct
N7	8	144: Pascal_1973-2002/Dec W1
N8	8	399: CA SEARCH(R)_1967-2002/UD=13723
N9	1	65: Inside Conferences_1993-2002/Dec W1 N10
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1	143: Biol. & Agric. Index_1983-2002/Oct N13	1 156: ToxFile_1965-2002/Nov W3
N14	1	172: EMBASE Alert_2002/Dec W1
N15	0	6: NTIS_1964-2002/Dec W1
N16	0	40: Enviroline(R)_1975-2002/Nov
N17	0	68: Env.Bib._1972-2002/Jun
N18	0	103: Energy SciTec_1974-2002/Nov B2
N19	0	305: Analytical Abstracts_1980-2002/Nov W3
N20	0	369: New Scientist_1994-2002/Oct W3

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$1.98 Estimated cost File411
$0.65 TELNET
$2.63 Estimated cost this search
$2.63 Estimated total session cost 1.360 DialUnits
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	619546	EXPRESSION
S1	23	FSH()(INDUCED OR INDUCES)(2N) EXPRESSION

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1/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13605780 22233373 PMID: 12297550
Relationship between steroidogenic acute regulatory protein expression and progesterone production in hen granulosa cells during follicle development.
Johnson A L; Solovieva E V; Bridgham J T
Department of Biological Sciences, The University of Notre Dame, Notre Dame, Indiana 46556.
Biology of reproduction (United States) Oct 2002, 67 (4) p1313-20, ISSN 0006-3363 Journal Code: 0207224
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
The present studies were conducted to address cellular mechanisms responsible for regulating steroidogenic acute regulatory protein (StAR) expression and progesterone synthesis at maturational stages corresponding to both the time of hen follicle selection, as well as before and after the LH surge in preovulatory follicle granulosa cells. A recently published report has established that mitogen-activated protein (MAP) kinase signaling induced by transforming growth factor alpha (TGFalpha) treatment blocks FSH-induced differentiation and StAR expression in cultured hen granulosa cells, whereas inhibitors of MAP kinase signaling enhance FSH-induced differentiation. The present in vitro studies demonstrate that in addition to MAP kinase signaling, activation of protein kinase C (PKC) blocks both *FSH*-*induced* StAR *expression* and the initiation of progesterone production in prehierarchal follicle granulosa cells, whereas the pharmacologic inhibitor of PKC, GF109203X, potentiates *FSH*-*induced* StAR *expression* and, as a consequence, the initiation of progesterone synthesis. Moreover, we demonstrate in granulosa cells collected from preovulatory follicles that although an acute increase in progesterone production in response to LH treatment requires rapid transcription and translation of StAR, the magnitude of progesterone production is rate-limited by one or more factors other than StAR (e.g., the P450 cholesterol side-chain enzyme). Finally, the rapid turnover of StAR protein, such as occurs following the withdrawal of LH, provides an additional mechanism for the tight regulation of progesterone production that occurs during the hen ovulatory cycle, and explains the rapid loss of steroidogenesis in the postovulatory follicle. In summary, data reported herein support the proposal that paracrine/autocrine factors (including but not necessarily limited to TGFalpha) prevent premature expression of StAR in prehierarchal follicle granulosa cells by more than one receptor-mediated signaling pathway. Furthermore, subsequent to follicle selection into the preovulatory hierarchy, StAR transcription and translation is necessary but not sufficient for the full potentiation of the preovulatory surge of serum progesterone.

1/3,AB/2 (Item 2 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

13400611 22067497 PMID: 12072408
Involvement of inhibitory nuclear factor-kappaB (NFkappaB)-independent NFkappaB activation in the gonadotropic regulation of X-linked inhibitor of apoptosis expression during ovarian follicular development in vitro. Wang Yifang; Chan Simon; Tsang Benjamin K
Reproductive Biology Unit and Division of Reproductive Medicine, Department of Obstetrics and Gynecology, University of Ottawa, Ottawa Health Research Institute, The Ottawa Hospital (Civic Campus), Ontario, Canada K1Y 4E9.
Endocrinology (United States) Jul 2002, 143 (7) p2732-40, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Increased X-linked inhibitor of apoptosis (XIAP) expression and suppressed follicular apoptosis are important determinants in the regulation of follicular development by FSH. The objective of the present study was to examine the role and regulation of nuclear factor-kappaB (NFkappaB) in the gonadotropic control of granulosa cell XIAP expression and follicular growth in vitro. FSH (100 ng/ml) increased rat granulosa cell XIAP mRNA abundance and protein content. The gonadotropin also induced granulosa cell p65 subunit-containing NFkappaB translocation from cytoplasm to nucleus and increased NFkappaB-DNA binding activity. Supershift EMSA indicated the FSH-activated NFkappaB contained p65 and p50 subunits. Unlike TNFalpha, FSH failed to elicit a significant change in granulosa cell phospho- and total-inhibitory NFkappaB (IkappaB) IkappaB contents in vitro and dominant-negative IkappaB expression was ineffective in blocking the increase in NFkappaB-DNA-binding activity and XIAP protein content induced by the gonadotropin. In contrast, SN50 (a cell permeable inhibitory peptide of NFkappaB translocation, 50-200 ng/ml) suppressed FSH-stimulated NFkappaB-DNA binding, XIAP expression, and follicular growth. FSH also increased granulosa cell phospho-Akt contents, a response sensitive to the PI-3K inhibitor LY294002 (10 microM). In conclusion, the present studies demonstrate that the *FSH*-*induced* XIAP *expression* is mediated through the NFkappaB pathway through activation of phosphatidylinositol 3-kinase rather than the classical IkappaB kinase.

1/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13311210 22082186 PMID: 12087075
FSH and LH induce progesterone production and progesterone receptor synthesis in cumulus cells: a requirement for meiotic resumption in porcine oocytes.
Shimada Masayuki; Terada Takato
Faculty of Applied Biological Science, Hiroshima University, Higashi-Hiroshima, Hiroshima, 739-8528, Japan.
Molecular human reproduction (England) Jul 2002, 8 (7) p612-8, ISSN 1360-9947 Journal Code: 9513710
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
The aim of this study was to investigate the role of progesterone in the meiotic resumption of porcine oocytes. Progesterone production and progesterone receptor (PR) immunoreactivity in cumulus cells were not detected in porcine cumulus-oocyte complexes (COC) when observations were made either just after collection from the follicles or after 28 h cultivation without LH and FSH. However, the addition of LH and *FSH* *induced* PR *expression* in cumulus cells, concomitant with increased progesterone production. To assess the role of progesterone in the COC, an inhibitor of progesterone production, aminoglutethimide (AGT), was administered. The addition of AGT to the medium with LH and FSH significantly suppressed progesterone production in a dose-dependent fashion. When COC were cultured with LH, FSH and 0.5x10(-3) mol/l AGT, almost complete inhibition of progesterone production and of germinal vesicle breakdown (GVBD) was seen. However, this inhibitory effect on GVBD was overcome by additional progesterone. Moreover, 0.5x10(-3) mol/l AGT also suppressed the reduction in connexin43, a gap junctional protein, in cumulus cells after 28 h cultivation, and increased the level of cyclic AMP in oocytes. These results support the hypothesis that the binding of progesterone, which was secreted by LH- and FSH-stimulated cumulus cells, to its newly synthesized receptor induces GVBD in porcine oocytes, possibly through a reduction of connexin43 in cumulus cells.

1/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13244383 22002282 PMID: 12006093
Regulation of expression of ovarian mRNA encoding steroidogenic enzymes and gonadotrophin receptors by FSH and GH in hypogonadotrophic cattle. Garverick H A; Baxter G; Gong J; Armstrong D G; Campbell B K; Gutierrez C G; Webb R
Department of Animal Sciences, University of Missouri, Columbia 65211, USA. GarverickA@missouri.edu
Reproduction (Cambridge, England) (England) May 2002, 123 (5) p651-61, ISSN 1470-1626 Journal Code: 100966036
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A study was conducted to determine the effects of FSH and bovine somatotrophin on the expression of mRNA encoding the gonadotrophin receptors and steroidogenic enzymes in ovarian follicles of cattle rendered hypogonadotrophic by treatment with a GnRH agonist. Hereford x Friesian heifers were allotted into two pretreatment groups: controls (n = 10) and GnRH agonist-treated (n = 20). Ovaries of control cows were removed on day 2 of the first follicular wave after synchronized oestrus. GnRH agonist-treated heifers were given either FSH or no FSH. FSH was infused at 50 microg h(-1) for 48 h. Ovaries in GnRH agonist-treated heifers were removed at the end of exogenous hormone treatment. The control, GnRH agonist and GnRH agonist plus FSH treatment groups were divided further into bovine somatotrophin or no bovine somatotrophin treatments (n = 5 per treatment). Bovine somatotrophin (25 mg day(-1) by s.c. injection) was administered for 3 days. Ovaries were scanned once a day by ultrasonography. Blood samples for hormone measurements were collected three times a day from oestrus until the time of removal of ovaries. Expression of mRNAs for the FSH and LH receptors and cytochrome P450 side-chain cleavage (P450scc), cytochrome P450 17alpha-hydroxylase (P450c17) and cytochrome P450 aromatase (P450arom) enzymes was

localized by in situ hybridization and quantified by image analysis. Ovarian follicular growth was arrested at < or = 4.5 mm in diameter in GnRH agonist-treated heifers. There was no effect of bovine somatotrophin on follicular dynamics, gonadotrophin secretion or expression of mRNA for either the gonadotrophin receptors or steroidogenic enzymes. Infusion of FSH to GnRH agonist-treated heifers increased FSH concentrations in serum to the physiological concentrations observed in controls and stimulated growth of follicles to a size similar (5.5-8.0 mm in diameter) to recruited follicles in control cows. *FSH* *induced* mRNA *expression* of P450scc and P450arom in granulosa cells of follicles at a smaller size (< or = 4.5 mm in diameter) than in controls and increased (P < 0.001) expression in larger (> 4.5 mm in diameter) follicles. Expression of mRNAs for P450scc and P450c17 increased (P < 0.001) with increasing follicle size and was higher (P < 0.01) in theca cells of GnRH agonist plus FSH-treated heifers than in the other groups. There were no treatment differences in expression of FSH receptor in granulosa cells or LH receptor in theca cells, but expression of both receptors increased with follicle size. There was no expression of LH receptor in the granulosa cells of cows from any treatment group. In conclusion, FSH treatment in GnRH agonist-treated heifers induced similar changes in follicular growth to those observed during the first follicular wave, but despite similar peak concentrations, prolonged exposure to high *FSH* *induced* precocious *expression* of mRNAs for P450scc and P450arom in granulosa cells from small follicles and markedly upregulated expression of these enzymes in granulosa cells from recruited follicles. The results of this study demonstrate the key role that FSH plays in the induction of follicular growth and differentiation.

1/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13225861 22015290 PMID: 12021046
Involvement of transforming growth factor alpha in the regulation of rat ovarian X-linked inhibitor of apoptosis protein expression and follicular growth by follicle-stimulating hormone.
Wang Yifang; Asselin Eric; Tsang Benjamin K
Division of Reproductive Medicine, Department of Obstetrics & Gynecology and Cellular & Molecular Medicine, University of Ottawa, Ottawa Health Research Institute, The Ottawa Hospital, Ottawa, Ontario, Canada K1Y 4E9. Biology of reproduction (United States) Jun 2002, 66 (6) p1672-80, ISSN 0006-3363 Journal Code: 0207224
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
The expression of X-linked inhibitor of apoptosis protein (XIAP), a member of a family of intracellular antiapoptotic proteins, is induced by FSH during follicular development in vivo. Whether the XIAP up-regulation by FSH (100 ng/ml) is a direct action of the gonadotropin and is important in the control of granulosa cell proliferation during follicular growth is unclear. The overall objective of the present study was to examine whether the *FSH*-*induced* XIAP *expression* and granulosa cell proliferation during follicular development is mediated by the secretion and action of intraovarian transforming growth factor alpha (TGFalpha). In rat follicles cultured for 2 and 4 days, FSH stimulated estradiol production, TGFalpha secretion, XIAP expression, and follicular growth. The theca cells are the primary follicular source of FSH-induced TGFalpha, as indicated by in situ hybridization. Intrafollicular injection of a neutralizing anti-TGFalpha antibody (50-200 ng/ml; immunoglobulin G as control) or addition of estradiol-antagonist ICI 182780 (0.5-100 nM) to the culture media suppressed *FSH*-*induced* XIAP *expression* and follicular growth. The effect of ICI 182780 could be partially reversed by high concentrations of estrogen (250 and 500 nM). Whereas TGFalpha (10-20 ng/ml) significantly increased granulosa cell XIAP content and proliferation in primary granulosa cell cultures, FSH alone was ineffective in eliciting the mitogenic response. Our results support the hypothesis that FSH stimulates granulosa cell proliferation via theca TGFalpha secretion and action in response to increased granulosa cell estradiol synthesis, and that XIAP up-regulation in response to FSH suppresses granulosa cell apoptosis and facilitates FSH-induced follicular growth.

1/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10819849 20374680 PMID: 10915218
Inhibitory effect of retinoic acid on the development of immature porcine granulosa cells to mature cells.
Hattori M; Takesue K; Nishida N; Kato Y; Fujihara N
Laboratory of Reproductive Physiology, Graduate School of Bioresource and Bioenvironmental Sciences, Kyushu University, Hakozaki, Fukuoka 812-8581, Japan. mhattori@agr.kyushu-u.ac.jp
Journal of molecular endocrinology (ENGLAND) Aug 2000, 25 (1) p53-61 , ISSN 0952-5041 Journal Code: 8902617
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The present study investigated the effect of retinoic acid (RA) on the differentiation of granulosa cells prepared from porcine ovaries. The granulosa cells were precultured for 15 h, then cultured for 48 h with FSH and further treated for 24 h with LH in order to induce their transformation into luteal cells. After the cells had been exposed to 1 microM retinoids (RA, retinal and retinol) for 87 h, analysis of the LH receptor mRNA expression, an indicator of granulosa cell differentiation, was carried out by using semiquantitative RT-PCR. The results showed that there was a decrease in LH receptor mRNA levels, and that RA had a more potent effect on these levels than the other two retinoids. When cells were exposed to RA in the immature stage (before the addition of FSH) or the early stage of development (0-24 h after the addition of FSH), expression of LH receptor mRNA was greatly diminished. When the immature cells were cultured for 15 h with RA, then washed and cultured for 48 h with FSH and for 24 h with LH, the expression of LH receptor mRNA was not reversed. In the differentiated cells (24 h after the addition of FSH), however, RA no longer had any inhibitory effect. When the immature cells were exposed to RA, *FSH*-*induced* *expression* of c-fos mRNA was markedly decreased. In contrast, expression of c-jun and activating transcription factor-4 mRNAs remained constant. However, the expression of c-fos mRNA was not decreased by forskolin. The results indicate that RA is a potent inhibitor in the immature stage of porcine granulosa cell differentiation, probably through decreased expression of FSH receptor, but that RA does not inhibit differentiation in the mature stage of the cells.

1/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10809611 20373869 PMID: 10919260
Role of winged helix transcription factor (WIN) in the regulation of Sertoli cell differentiated functions: WIN acts as an early event gene for follicle-stimulating hormone.
Chaudhary J; Mosher R; Kim G; Skinner M K
Center for Reproductive Biology, Washington State University School of Molecular Biosciences, Pullman 99164-4231, USA.
Endocrinology (UNITED STATES) Aug 2000, 141 (8) p2758-66, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Members of the winged helix transcription factor family are known to regulate epithelial cell differentiation by regulating cell-specific gene expression. rWIN is a newly discovered member of the winged helix family shown to be present in the adult rat testis. In the testis the human homolog of rWIN, HFH-11, was localized to the germ cells (i.e. spermatocytes and spermatids) undergoing spermatogenesis. In the present study we show that rWIN is also expressed in testicular Sertoli cells. Sertoli cells are the epithelial component of the seminiferous tubule and provide both the cytoarchitectural support and the microenvironment for developing germ cells. The presence of rWIN in Sertoli cells was confirmed by Northern blot and RT-PCR analysis. The rWIN transcript size in the Sertoli cells was different from the germ cell transcript that is probably due to alternative splicing or modifications of the 3'-untranslated region. At least two spliced variants of rWIN were observed in the Sertoli cells corresponding to the deletion of an exon in the DNA-binding region. Long term stimulation of cultured Sertoli cells with the gonadotropin FSH down-regulated rWIN expression. In contrast, short-term stimulation (2 h) transiently up-regulated rWIN *expression*. The *FSH*-*induced* transient stimulation of rWIN precedes expression of the transferrin gene that is a marker of Sertoli cell differentiation. FSH-induced transferrin promoter activity was inhibited when cultured Sertoli cells were treated with an antisense oligonucleotide to rWIN. Interestingly, the constitutive overexpression of the DNA-binding domain of rWIN also down-regulated transferrin promoter activity. Analysis of the transferrin promoter with various deletion mutations suggested that rWIN acts at an upstream gene of the transferrin promoter. The results indicate that a transient up-regulation of rWIN in part mediates the ability of FSH to activate the transferrin promoter, which can be inhibited with a rWIN antisense oligonucleotide or constitutive expression of the rWIN DNA-binding domain. The current study demonstrates that rWIN acts as an early event gene for FSH actions on Sertoli cells and that rWIN appears to have a role in the regulation of Sertoli cell differentiated functions.

1/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10068548 99047422 PMID: 9828191
Factors affecting the developmental competence of mouse oocytes grown in vitro: follicle-stimulating hormone and insulin.
Eppig J J; O'Brien M J; Pendola F L; Watanabe S
The Jackson Laboratory, Bar Harbor, Maine 04609-1500, USA. jje@jax.org Biology of reproduction (UNITED STATES) Dec 1998, 59 (6) p1445-53, ISSN 0006-3363 Journal Code: 0207224
Contract/Grant No.: CA34196; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
This study was undertaken to test the hypothesis that FSH treatment of cultured oocyte-granulosa cell complexes promotes acquisition of competence to complete preimplantation embryo development. Oocyte-granulosa cell complexes were isolated from the preantral follicles of 12-day-old mice and cultured for 10 days in serum-free medium, supplemented with insulin (5 microgram/ml), transferrin (5 microgram/ml), and selenium (5 ng/ml) and containing a highly potent preparation of FSH (0-5 ng/ml). Oocytes were matured and fertilized in vitro and embryos cultured to determine the frequency of development to the blastocyst stage. There was no effect of FSH on oocyte size, general morphology, or competence to resume meiosis. However, addition of FSH to medium containing insulin had a deleterious effect on the percentage of mature oocytes competent to develop to the blastocyst stage. Deletion of insulin from the medium for culture of oocyte-granulosa cell complexes prevented the deleterious effect of FSH, but FSH still did not promote acquisition of competence to complete preimplantation development. Culture of oocyte-granulosa cell complexes with FSH resulted in elevated expression of LH receptor (LHR) mRNA by granulosa cells and stimulated the production of functional LHRs, whether or not insulin was present. However, *FSH*-*induced* *expression* of LHR mRNA reached a maximum steady-state level by 4 days of culture in the presence of insulin, but this level was not reached until 10 days of culture without insulin. Granulosa cells encompassing growing mouse oocytes in vivo do not express LHR mRNA. Thus, expression of LHR mRNA by granulosa cells closely associated with growing oocytes in vitro indicates inappropriate or ambiguous development. In conclusion, conditions occurring during oocyte growth can have profound detrimental effects on oocyte developmental competence to complete preimplantation development, even when oocyte growth, general morphology, and competence to resume meiosis appear unaffected.

1/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09719208 98152085 PMID: 9491385
Mouse oocytes suppress cAMP-induced expression of LH receptor mRNA by granulosa cells in vitro.
Eppig J J; Pendola F L; Wigglesworth K
Jackson Laboratory, Bar Harbor, Maine 04609, USA. jje@aretha.jax.org Molecular reproduction and development (UNITED STATES) Mar 1998, 49 (3) p327-32, ISSN 1040-452X Journal Code: 8903333
Contract/Grant No.: CA34196; CA; NCI; HD23839; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Mouse oocytes suppress follicle-stimulating hormone (FSH)-induced luteinizing hormone receptor (LHR) messenger ribonucleic acid (mRNA) expression in cultured granulosa cells. The objective of this study was to assess the mechanism by which oocytes suppress *FSH*-*induced* LHR *expression* . The effect of cumulus cell-denuded, germinal-vesicle-stage oocytes, isolated from antral follicles,

on FSH-induced cyclic adenosine monophosphate (cAMP) production by cultured granulosa cells was determined by radioimmunoassays. In addition, the effect of oocytes on 8Br-cAMP-induced LHR mRNA steady-state expression by granulosa cells was assessed by RNase protection assays. Oocytes had no detectable effect on FSH-induced cAMP production. However, oocytes dramatically suppressed 8Br-cAMP-induced LHR mRNA steady-state expression by granulosa cells. It was concluded that the mechanism by which oocytes suppress *FSH*-*induced* steady-state *expression* of LHR mRNA is not by inactivating FSH, preventing functional interactions of FSH with its granulosa cell receptors, or by interfering with the signal-transduction mechanisms required for FSH-dependent cAMP production. In addition, since oocytes suppressed the 8Br-cAMP-induced increase in steady-state expression of mRNA for LHR, oocyte-derived factors probably suppress expression by acting downstream of FSH-induced elevation of granulosa cell cAMP.

1/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09368675 97251199 PMID: 9096881
Murine oocytes suppress expression of luteinizing hormone receptor messenger ribonucleic acid by granulosa cells.
Eppig J J; Wigglesworth K; Pendola F; Hirao Y
Jackson Laboratory, Bar Harbor, Maine 04609-1500, USA. jje@aretha.jax.org Biology of reproduction (UNITED STATES) Apr 1997, 56 (4) p976-84, ISSN 0006-3363 Journal Code: 0207224
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
This study tested the hypothesis that murine oocytes participate in the establishment of granulosa cell phenotypic heterogeneity in preovulatory follicles. In these follicles, mural granulosa cells express LH receptors (LHR) and LHR mRNA, but expression of these molecules is low or undetectable in cumulus cells. Thus, the expression of LHR mRNA is a marker of the mural granulosa cell phenotype in preovulatory follicles. Cumulus cells expressed elevated steady-state levels of LHR mRNA when oocytes were microsurgically removed from oocyte-cumulus cell complexes, and this was prevented by paracrine factor(s) secreted by isolated oocytes. These factors also suppressed FSH-induced elevation of the level of LHR mRNA expression by mural granulosa cells isolated from small antral follicles, even when expression was augmented by culturing granulosa cells on components of basal lamina. Moreover, factor(s) secreted by oocytes suppressed the expression of LHR mRNA in mural granulosa cells isolated from preovulatory follicles already expressing elevated levels of these transcripts. The ability of oocytes to suppress the LHR mRNA expression by granulosa cells was developmentally regulated. Oocytes from preantral follicles and mature (metaphase II arrested) oocytes were less effective in suppressing expression than fully grown, germinal vesicle (GV)-stage oocytes. Furthermore, two-cell-stage embryos did not suppress LHR mRNA levels. Coculture of isolated oocytes with granulosa cells affected the synthesis of very few granulosa cell proteins detected by fluorography of two-dimensional gels after 35S-methionine labeling. Thus, oocyte suppression of *FSH*-*induced* LHR mRNA *expression* is specific in both the suppressing cell type and the effects on granulosa cells. It is concluded that the default pathway of granulosa cell differentiation produces the mural granulosa cell phenotype, as represented by the expression of LHR mRNA. This pathway is abrogated by oocytes. Thus, oocytes play a dominant role in establishing the fundamental heterogeneity of the granulosa cell population of preovulatory follicles.

1/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08812050 96174909 PMID: 8592519
A role for increased lutropin/choriogonadotropin receptor (LHR) gene transcription in the follitropin-stimulated induction of the LHR in granulosa cells.
Shi H; Segaloff D L
Department of Physiology, University of Iowa College of Medicine, Iowa City 52242, USA.
Molecular endocrinology (Baltimore, Md.) (UNITED STATES) Jun 1995, 9 (6) p734-44, ISSN 0888-8809 Journal Code: 8801431
Contract/Grant No.: DK-25295; DK; NIDDK; HD-00968; HD; NICHD; HD-22196; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Follitropin (FSH) has been shown in previous studies to stimulate the induction of the LH/CG receptor (LHR) and LHR mRNA in the granulosa cells of diethylstilbesterol-primed immature rats. The present studies were undertaken to identify the mechanisms underlying the hormone-dependent induction of the LHR in rat granulosa cells. The effect of FSH on LHR mRNA stability was determined by measuring the decay of LHR mRNA after removal of FSH under conditions where transcription was inhibited. Under these conditions, readdition of FSH had little effect on mRNA stability. However, inhibitors of transcription themselves were found to have a marked effect on stabilizing the LHR mRNA, thus potentially masking an effect of FSH. These results suggest that there is a labile destabilizing factor that constitutively degrades LHR mRNA. At present, it cannot be ascertained whether FSH has any effect on this destabilizing factor. Transcriptional activity of the LHR gene was examined using nuclear run-on assays. It was found that 1) in the absence of FSH, LHR-binding activity and mRNA levels were negligible, but the LHR gene was transcriptionally active in granulosa cells of immature rats; 2) incubations of granulosa cells with FSH or 8-bromo-cAMP significantly increased endogenous LHR gene transcription (approximately 10-fold) under conditions where increases in LHR mRNA were observed; 3) the continuous presence of FSH or 8-bromo-cAMP was required to maintain elevated levels of LHR gene transcription and LHR mRNA; and 4) exogenous estradiol alone had no effect on transcription of the LHR gene although it was able to synergistically enhance *FSH*-*induced* LHR *expression*. These experiments suggest that while the effects of estradiol on LHR induction do not appear to be mediated by an increase in LHR gene transcription, the effects of FSH (or cAMP) on LHR induction are clearly mediated, at least in part, by significant increases in the rate of LHR gene transcription.

1/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08723965 96068678 PMID: 7479863
Pituitary follicle-stimulating hormone (*FSH*) *induces* CREM gene *expression* in Sertoli cells: involvement in long-term desensitization of the FSH receptor.
Monaco L; Foulkes N S; Sassone-Corsi P
Institut de Genetique et de Biologie Moleculaire et Cellulaire, Centre National de la Recherche Scientifique, Institut National de la Sante et de la Recherche Medicale, Universite Louis Pasteur, Strasbourg, France. Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Nov 7 1995, 92 (23) p10673-7, ISSN 0027-8424 Journal Code: 7505876
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Transcription factor CREM (cAMP-responsive element modulator) plays a pivotal role in the nuclear response to cAMP in neuroendocrine cells. We have previously shown that follicle-stimulating hormone (FSH) directs CREM expression in male germ cells. The physiological importance of FSH in Sertoli cell function prompted us to analyze its effect on CREM expression in these cells. We observed a dramatic and specific increase in the CREM isoform ICER (inducible cAMP early repressor) expression, with a peak 4 h after FSH treatment of primary Sertoli cells. Interestingly, induced levels of ICER protein persist for a considerably longer time. Induction of the repressor ICER accompanies early down-regulation of the FSH receptor transcript, which leads to long-term desensitization. Here we show that ICER represses FSH receptor expression by binding to a CRE-like sequence in the regulatory region of the gene. Our results confirm the crucial role played by CREM in hormonal control and suggest its role in the long-term desensitization phenomenon of peptide membrane receptors.

1/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08596177 95354569 PMID: 7628357
Regulation of 3 beta-hydroxysteroid dehydrogenase delta 5/delta 4-isomerase and cholesterol side-chain cleavage cytochrome P450 by activin in rat granulosa cells.
Miro F; Smyth C D; Whitelaw P F; Milne M; Hillier S G
Department of Obstetrics and Gynecology, University of Edinburgh Center for Reproductive Biology, Scotland.
Endocrinology (UNITED STATES) Aug 1995, 136 (8) p3247-52, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Activin is a dimeric protein implicated in the local control of follicular steroidogenesis. Using cultured rat granulosa cells, we previously showed that the effect of activin on FSH-induced progesterone synthesis changes with preovulatory follicular development, from positive regulation in nondifferentiated (immature) granulosa cells to negative regulation in preovulatory (mature) granulosa cells. The aim of the present study was to assess development-related effects of activin on the expression of enzymes crucial to progesterone synthesis: cholesterol side-chain cleavage cytochrome P450 (P450scc) and 3 beta-hydroxysteroid dehydrogenase/delta 5-4-isomerase (3 beta HSD). Nondifferentiated granulosa cells were isolated from the ovaries of estrogen-pretreated immature female rats that received no other treatment; differentiated granulosa cells were obtained from similar animals treated for 48 h with human FSH to induce preovulatory follicular development. Cells were cultured for 48 h in serum-free medium with and without human FSH and/or recombinant activin-A, and medium was collected for measurement of progestagens (progesterone, pregnenolone, and 20 alpha-dihydroprogesterone). In cultures of nondifferentiated granulosa cells, activin augmented the FSH-induced production of all three steroids. In differentiated granulosa cells, activin suppressed the FSH-stimulated production of progesterone and 20 alpha-dihydroprogesterone, but had no effect on pregnenolone. The presence of exogenous pregnenolone increased the overall production of progesterone, but did not alter qualitative steroidogenic responses to activin. To assess the interaction between FSH and activin on 3 beta HSD and P450scc messenger RNA (mRNA) expression, Northern blot analyses were performed on total RNA isolated from cultured granulosa cells. Treatment in vitro with FSH alone markedly enhanced the abundance of both the 3 beta HSD and P450scc mRNA transcripts in nondifferentiated and differentiated granulosa cells. FSH-stimulated expression of P450scc mRNA was further enhanced by cotreatment of nondifferentiated granulosa cells with activin. However, activin had no consistent effect on FSH-stimulated expression of 3 beta HSD mRNA in nondifferentiated cells. In differentiated granulosa cells, both mRNAs were suppressed more than 50% by the presence of activin. We conclude that the in vitro effects of activin on *FSH*-*induced* *expression* of 3 beta HSD and P450scc mRNAs in rat GC are similar: initially stimulatory (P450scc) or without effect (3 beta HSD), then becoming completely inhibitory. The mechanism of this development-dependent change in the granulosa cell response to activin remains to be elucidated.

1/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08343352 95100713 PMID: 7802429
[Intragonadal regulation of human follicular genesis: facts and hypotheses]
Regulation intragonadique de la folliculogenese humaine: faits et hypotheses.
Gougeon A
INSERM U-355, Clamart.
Annales d'endocrinologie (FRANCE) 1994, 55 (2) p63-73, ISSN 0003-4266 Journal Code: 0116744
Document type: Congresses; Review; Review, Academic ; English Abstract Languages: FRENCH
Main Citation Owner: NLM
Record type: Completed
In the mammalian ovary, the follicular growth is classically considered to be under the control of pituitary gonadotropins. In the human, three cycles (85 days) are required for a preantral follicle (approximately 0.15 mm in diameter) to attain the ovulatory size (approximately 20 mm in diameter). During this growing phase, follicular responsiveness to LH and especially to FSH exhibits strong changes. Up to diameter of approximately 2mm, follicles are unsensitive to cyclic changes in circulating levels of FSH, in terms of quality, growth rate and steroidogenesis (basal follicular growth). Follicles larger than 2 mm become responsive to FSH, in terms of quality and growth rate, but their ability to synthesize estrogen remains very low,

they constitute the population of recruitable follicles. From its selection, the follicle destined to ovulate becomes mores and more responsive, first to FSH and then to LH; all the gonadotropin-induced functions are expressed during preovulatory maturation. The aim of this review is to clarify the intraovarian regulations involved: (a) in the inhibition of gonadotropin-induced functions (basal follicular growth); (b) in the acceleration of the growth rate of recruitable follicles and simultaneous acquisition of FSH responsiveness of their granulosa cells during the late luteal phase, as well as in the "selection" of one of them; (c) in the strong proliferation of granulosa cells paralleling with full *expression* of *FSH*-*induced* functions (preovulatory maturation before LH surge) and (d) in the inhibition of granulosa cell proliferation paralleling with full expression of FSH- and LH-induced functions (preovulatory maturation after the LH surge). Some peptides and proteins, such as growth factors (EGF, IGFs et IGFBPs, TGF-beta), the inhibin-activin-follistatin system and TNF-alpha, and synthesized by the follicular tissues, might be involved in both the inhibition and stimulation of follicular responsiveness to gonadotropins. Their possible role during maturation of the primate follicle has been analyzed in the light of the most recent findings.

1/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07611694 93121946 PMID: 8380382
Tyrphostins inhibit follicle-stimulating hormone-mediated functions in cultured rat ovarian granulosa cells.
Gomberg-Malool S; Ziv R; Re'em Y; Posner I; Levitzki A; Orly J
Department of Biological Chemistry, Alexander Silberman Institute of Life Sciences, Hebrew University of Jerusalem, Israel.
Endocrinology (UNITED STATES) Jan 1993, 132 (1) p362-70, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
FSH *induces* the *expression* of cholesterol side-chain cleavage cytochrome P450 (P450scc) in rat ovarian granulosa cells. The present study reveals that the tyrphostin AG18, a member of novel protein tyrosine kinase inhibitors, can arrest the FSH-induced synthesis of P450scc with an apparent IC50 of 30 microM. Total inhibition of P450scc expression was achieved at 80 microM AG18. AG18-mediated inhibition of P450scc was also observed when the enzyme was induced by prostaglandin E2, forskolin, or 8-bromo-cAMP. Studies examining functional LH receptors showed that the tyrphostin inhibits the *expression* of *FSH*-*induced* LH receptors. The drug did not affect FSH-induced cAMP accumulation, suggesting that it may interfere with the flow of FSH signal transduction at a site distal intracellular accumulation of cAMP. Control experiments demonstrated that the inhibitory action of AG18 was reversible, did not hamper total protein synthesis in the cells, and did not change the adenine nucleotide (ATP:ADP:AMP) ratio or their levels in the treated cells. A cell-free assay of cAMP-dependent protein kinase showed that the tyrphostin AG18 does not affect this enzyme activity up to concentrations above 200 microM. These results suggest that a putative tyrosine kinase activity is involved in the gonadotropin signal transduction pathway leading to expression of functional genes in ovarian cells.

1/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07588625 93109310 PMID: 8380222
Transcriptional regulation of the rat tissue type plasminogen activator gene: localization of DNA elements and nuclear factors mediating constitutive and cyclic AMP-induced expression.
Ohlsson M; Leonardsson G; Jia X C; Feng P; Ny T
Department of Applied Cell and Molecular Biology, University of Umea, Sweden.
Molecular and cellular biology (UNITED STATES) Jan 1993, 13 (1) p266-75, ISSN 0270-7306 Journal Code: 8109087
Contract/Grant No.: HD-12303; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have characterized tissue type plasminogen activator (tPA) promoter elements and nuclear factors required for follicle-stimulating hormone (FSH)-induced transcription of the rat tPA gene in granulosa cells and constitutive expression of the gene in the rat neuroblastoma cell line B103. Run-on transcription analysis of isolated nuclei revealed that B103 cells transcribe the tPA gene at a high and constitutive level, while FSH was found to induce tPA gene transcription in a rapid and transient manner in granulosa cells. The maximal FSH-induced transcription rate was obtained after 20 min and was similar in the absence or presence of the protein synthesis inhibitor cycloheximide. However, in the presence of cycloheximide, tPA transcription was not turned off but continued at a high rate for several hours. This phenomenon may at least partly explain the earlier finding that tPA mRNA is superinduced by FSH in the presence of cycloheximide. DNase I footprinting analysis of the first 621 bp of the tPA promoter revealed a total of six regions that interact with nuclear factors from B103 and granulosa cells. Deletion of the promoter region from positions -269 to -621, a region that includes the two most-upstream footprints, had no effect on constitutive or FSH-induced transcription in transient expression experiments. Nuclear extracts from both granulosa cells and B103 cells showed strong binding to a consensus cyclic AMP-responsive element (CRE) at positions -178 to -185 and a neighboring binding site for nuclear factor 1 (NF1) at positions -145 to -158. The factors binding to these two regions were identified as members of the CRE-binding protein and NF1 families of transcription factors, respectively. Footprints were also obtained over two GC boxes at positions -64 to -71 and -41 to -49. These footprints were more pronounced with nuclear extracts from B103 cells than with extracts from untreated or FSH-treated granulosa cells, but gel shift assays indicate that similar amounts of two distinct factors bind to the two GC boxes in both cell types. Transfection experiments using promoter constructs with inactivated promoter elements indicate that both the CRE and NF1 sites contribute to the FSH responsiveness of the rat tPA gene in granulosa cells, while only the NF1 site is important for constitutive expression in B103 cells. The two GC boxes were found to be necessary both for constitutive expression in B103 cells and for *FSH*-*induced* *expression* in granulosa cells, and inactivation of both GC boxes essentially eliminated the tPA promoter activity in both cell types.

1/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07240136 92184003 PMID: 1665832
Tumor-promoting phorbol ester acts synergistically with insulin to induce lutropin receptor expression in rat granulosa cells.
Hattori M; Takahashi M; Horiuchi R
Department of Pharmaceutical Chemistry, Gunma University, Maebashi, Japan.
Molecular and cellular endocrinology (NETHERLANDS) Oct 1991, 81 (1-3) p69-76, ISSN 0303-7207 Journal Code: 7500844
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Lutropin (LH) receptors in rat granulosa cells are expressed by activation of cAMP-dependent protein kinase in response to follitropin (FSH). In the present study, 12-O-tetradecanoylphorbol 13-acetate (TPA) could cause a dose-dependent expression of LH receptors in the presence of insulin, but not in the absence of insulin, as measured by binding of 125I-deglycosylated human choriogonadotropin (DGhCG). The synergistic action of TPA with insulin was achieved at 1 nM and 10 mIU/ml, respectively. The receptor expression induced by this synergistic action was accompanied by cAMP accumulation which was detected after a lag time of 6 h following exposure to TPA. However, a synthetic diacylglycerol and non-protein kinase C activating phorbol derivatives did not mimic the effect of TPA on the receptor expression. In addition, insulin modulated the inhibitory effect of TPA in *FSH*-*induced* LH receptor *expression* , indicating a peculiar action of insulin in the receptor expression. Indomethacin treatment led to a dose-dependent inhibition in the receptor expression in the cells treated with TPA plus insulin more than that in the cells with FSH plus insulin, suggesting that the synergistic action was dependent upon cyclooxygenase and/or phospholipase A2 activity. It was shown by Scatchard analysis of LH receptors and kinetic studies of hCG-stimulated cAMP formation that the synergistic action of TPA with insulin led to expression of functional LH receptors coupled with the adenylate cyclase system in cultured granulosa cells.

1/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07130281 92064128 PMID: 1659543
Follicle-stimulating hormone increases c-fos mRNA levels in rat granulosa cells via a protein kinase C-dependent mechanism.
Pennybacker M; Herman B
Department of Cell Biology and Anatomy, University of North Carolina, Chapel Hill 27599.
Molecular and cellular endocrinology (NETHERLANDS) Sep 1991, 80 (1-3) p11-20, ISSN 0303-7207 Journal Code: 7500844
Contract/Grant No.: 2-P01-CA29589; CA; NCI; AG07218; AG; NIA; AG10104; AG ; NIA
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Recent evidence has been presented that follicle-stimulating hormone (FSH) stimulates the induction of granulosa cell c-fos protooncogene mRNA in vivo (Pennybacker and Herman (1989) J. Cell Biol. 109, 151A; Delidow et al. (1990) Endocrinology 126, 2302-2306), yet the mechanisms by which FSH induces c-fos mRNA expression have not been delineated. To elucidate the mechanisms of FSH-dependent c-fos mRNA expression, we measured the time and dose dependence of c-fos mRNA levels using Northern blot analysis in intact ovaries and cultured granulosa cells in response to FSH. In intact ovaries, FSH-induced c-fos mRNA expression was time dependent with maximal expression at 90 min post FSH injection, while in cultures of granulosa cells obtained from estrogen-primed immature female rats, c-fos mRNA levels were highest after 30 min exposure to FSH and at a concentration of 100 ng/ml. Neither 8-bromo adenosine 3',5'-cyclic monophosphate (8-br-cAMP), at doses ranging from 0.1 to 10 mM, nor 100 microM forskolin (in the presence or absence of 200 microM isobutyl-methylxanthine) or luteinizing hormone (LH, 100 ng/ml) were able to mimic FSH-induced c-fos mRNA expression in granulosa cell cultures. However, tetradecanoyl-13-phorbol acetate (TPA, 200 nM) was able to induce c-fos mRNA expression. The protein kinase C (PKC) inhibitors H-7 (0.3-30 microM) and staurosporine (0.75 micrograms/ml) blocked FSH-induced c-fos mRNA expression in cultured granulosa cells while HA 1004, an inhibitor of cGMP- and cAMP-dependent protein kinases at 30 microM had no effect on TPA-induced c-fos expression, and only minimally inhibited *FSH*-*induced* c-fos *expression* . Both FSH (100 ng/ml) and forskolin (3 microM) increased progesterone production in cultured granulosa cells. These data support the hypothesis that FSH specifically induces c-fos mRNA expression by a PKC-dependent mechanism and that the cAMP arm of the FSH response pathway is operant in these cells.

1/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06307331 89391956 PMID: 2551266
Tumor necrosis factor-alpha inhibits follicle-stimulating hormone-induced differentiation in cultured rat granulosa cells.
Darbon J M; Oury F; Laredo J; Bayard F
INSERM U168, Department of Endocrinology, CHU Rangueil, Universite Paul Sabatier, Toulouse, France.
Biochemical and biophysical research communications (UNITED STATES) Sep 15 1989, 163 (2) p1038-46, ISSN 0006-291X Journal Code: 0372516 Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have investigated the effects of TNF-alpha on *FSH*-*induced* LH receptor *expression*, cAMP and progesterone production in cultured rat granulosa cells. TNF-alpha (0.5-100 ng/ml) inhibits the stimulating action of FSH on LH receptor formation in a dose-dependent manner with an IC50 of 1 ng/ml and an almost complete suppression of LH receptor induction for 50-100 ng/ml TNF-alpha. The inhibitory effect of TNF-alpha is not due to variations in cell number or viability but rather to a reduction of the LH receptor content per cell with no change in binding affinity (KD = 0.8 x 10(-10)M). TNF-alpha also inhibits the FSH-induced cAMP production but at a lower extent, with a maximum reduction of 60% for 100 ng/ml TNF-alpha. Moreover, TNF-alpha impairs the LH receptor formation induced by forskolin, cholera toxin or 8-Bromo-cAMP, indicating that the cytokine also acts at a step distal to FSH

receptor and to cAMP formation. Finally, TNF-alpha decreases dramatically the progesterone synthesis that is stimulated by FSH, with a reduction to undetectable levels on and after 10 ng/ml TNF-alpha. These results suggest that TNF-alpha may drastically reduce the capacity of granulosa cells to differentiate upon FSH stimulation and to respond to LH during the physiological ovarian follicular maturation. Such anti-gonadotropic action of TNF-alpha on granulosa cell differentiation may be also relevant to the alteration of ovarian function during physiopathological processes like inflammatory or infection diseases.

1/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05963295 89050085 PMID: 2847713
Fibroblast growth factor regulates the expression of luteinizing hormone receptors in cultured rat granulosa cells.
Oury F; Darbon J M
Inserm U 168, Department of Endocrinology, CHU Rangueil, Universite Paul Sabatier, Toulouse, France.
Biochemical and biophysical research communications (UNITED STATES) Oct 31 1988, 156 (2) p634-43, ISSN 0006-291X Journal Code: 0372516 Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have investigated the effects of bFGF on both the *FSH*- *induced* LH receptor *expression* and cAMP production in cultured rat granulosa cells. Concentrations of pure FGF, from 10(-12) M to 10(-10) M, progressively inhibit the stimulatory actions of FSH with an ED50 of approximately 4 x 10(-12) M for both parameters. Higher FGF concentrations, from 4 x 10(-10) M to 10(-8) M, lead to a gradual reduction of the growth factor inhibitory effect. The effects of FGF are more prominent on the modulation of LH receptors than on the FSH-induced cAMP production. Moreover, FGF impairs the LH receptor formation induced by cholera toxin or 8-Bromo-cAMP, indicating that the growth factor also acts at a step distal to cAMP formation. The inhibitory effect of FGF on LH receptor expression increases during the entire course of granulosa cell differentiation, from 24 to 96 h, and is not due to variations in cell number or viability, but rather to a change in the content of LH receptors with no significant modification of binding affinity (KD congruent to 0.8 x 10(-10) M). These results suggest that bFGF may acutely regulate the capacity of granulosa cells to differentiate upon FSH stimulation and to respond to LH during the ovarian follicular maturation.

1/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05864340 88288216 PMID: 3135483
Follicle-stimulating hormone induces transient expression of the protooncogene c-fos in primary Sertoli cell cultures.
Hall S H; Joseph D R; French F S; Conti M
Department of Pediatrics and Physiology, University of North Carolina, Chapel Hill 27514.
Molecular endocrinology (Baltimore, Md.) (UNITED STATES) Jan 1988, 2 (1) p55-61, ISSN 0888-8809 Journal Code: 8801431
Contract/Grant No.: 5-P30-HD-18968; HD; NICHD; HD-20788; HD; NICHD; HD-21744; HD; NICHD; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The expression of the protooncogene c-fos has been associated with the transduction of cell surface stimuli into changes in nuclear function. To evaluate the possibility that this protooncogene plays a role in the gonadotropin-dependent gene regulation, the effect of FSH on the expression of c-fos was studied in primary Sertoli cell cultures. Sertoli cells were stimulated for different time intervals with FSH and c-fos mRNA levels measured by Northern RNA blot analysis. FSH treatment increased c-fos mRNA transiently with a maximal stimulation reached in 1 h. The level of c-fos mRNA returned to basal level within 4-6 h. The induction of c-fos mRNA was dependent on the concentration of FSH used with an ED50 of 3-5 ng/ml ovine FSH-16. A similar increase in c-fos expression was induced with highly purified hFSH. The c-fos mRNA was also elevated after treatment of the Sertoli cell with (Bu)2cAMP and forskolin. (Bu)2cAMP treatment led to a sustained induction of c-fos mRNA, with increased mRNA levels being maintained after 12 h. The FSH-dependent induction of c-fos mRNA was still present in cells treated for 3 h with cycloheximide, but it was greatly reduced by actinomycin D pretreatment. These data indicate that *FSH* *induces* a transient *expression* of c-fos in cultured Sertoli cells. This induction is probably mediated by cAMP and likely involves an increased transcription of the c-fos gene. Early expression of this gene might be an intermediate step required for gonadotropin-dependent regulation of expression of other genes.

1/3,AB/22 (Item 1 from file: 65)
DIALOG(R)File 65:Inside Conferences
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00731535 INSIDE CONFERENCE ITEM ID: CN007135087
FSH-*induced* c-fos *expression* and its relevance to androgen metabolism by Sertoli cells
Jia, M. C.; Ravindranath, N.; Papadopoulos, V.; Dym, M.
CONFERENCE: 76th Annual meeting
PROGRAM AND ABSTRACTS OF THE ANNUAL MEETING-ENDOCRINE SOCIETY , 1994; ISSUE 76 P: 987
The Endocrine Society Press, 1994
ISSN: NONE-XXXX ISBN: 1879225131
LANGUAGE: English DOCUMENT TYPE: Conference Abstracts and programme CONFERENCE SPONSOR: The Endocrine Society
CONFERENCE LOCATION: Anaheim, CA
CONFERENCE DATE: Jun 1994 (199406) (199406)
NOTE:
Also contains abstracts and programme from the 4th Annual symposium of the Endocrine Nurses Society

1/3,AB/23 (Item 1 from file: 94)
DIALOG(R)File 94:JICST-EPlus
(c)2002 Japan Science and Tech Corp(JST). All rts. reserv.
04118804 JICST ACCESSION NUMBER: 99A0694102 FILE SEGMENT: JICST-E Effects of Recombinant FSH Combined with hCG on the Ovaries of Immature Hypophysectomized Rats: Endocrinological, Light Microscopical and Immunohistochemical Studies.
OKAZAKI T (1); UEKI M (1); SUGIMOTO O (1); MORI H (1)

(1) Osaka Medical Coll., Osaka, Jpn
Bull Osaka Med Coll, 1998, VOL.44,NO.1, PAGE.31-42, FIG.5, TBL.3, REF.19 JOURNAL NUMBER: Z0447BBI ISSN NO: 0916-2844
UNIVERSAL DECIMAL CLASSIFICATION: 591.16.05+591.463/.467 577.175.3 LANGUAGE: English
COUNTRY OF PUBLICATION: Japan
DOCUMENT TYPE: Journal
ARTICLE TYPE: Original paper
MEDIA TYPE: Printed Publication
ABSTRACT: To examine the exact role of follicle-stimulating hormone (FSH) in the folliculogenesis and steroidogenesis, human recombinant FSH (rec-FSH) alone (40 IU in total) or with human chorionic gonadotropin (hCG: 0.1 or 1 IU in total) was administered subcutaneously to immature hypophysectomized rats (IH-rats) 11 days after hypophysectomy, twice daily for 4 days. The plasma progesterone levels increased in the IH-rats treated with rec-FSH alone, compared to the control IH-rats. The plasma estradiol levels in the IH-rats treated with rec-FSH alone were low, but significantly higher than those in the control IH-rats, and noticeably elevated in IH-rats treated with rec-FSH plus hCG. Histology showed that the treatment with rec-FSH alone enlarged the follicular size accompanied with thickened theca interna layer. An addition of hCG plus rec-FSH induced the proliferation and hypertrophy of theca interna cells in an hCG-dependent manner. The immunohistochemistry revealed that the immunoreaction for 3 .BETA.-hydroxysteroid dehydrogenase was localized intensely in the interstitial cells regardless of the presence or absence of FSH and hCG, and less intensely in oocytes, follicular fluid and atretic follicles. The theca interna cells became positive when 0.1 or 1 IU of hCG plus FSH was treated, and the granulosa cells were positive first when 1 IU of hCG plus FSH was given. The activity of 17 .ALPHA.-hydroxylase (17 .ALPHA.-H) was expressed in oocytes, follicular fluid and atretic follicles even in the control IH-rats. The immunoreaction in the follicular fluid became intense when rec-FSH alone or with hCG was treated. An addition of 0.1 IU of hCG plus *FSH* *induced* the *expression* of 17 .ALPHA.-H in the theca interna cells, and 1 IU of hCG in the interstitial cells. (author abst.)
? b 411
02dec02 13:42:18 User217743 Session D583.3
$0.23 0.073 DialUnits File155
$0.23 Estimated cost File155
$0.03 TELNET
$0.26 Estimated cost this search
$0.31 Estimated total session cost 0.304 DialUnits File 411:DIALINDEX(R)

DIALINDEX(R)
(c) 2002 The Dialog Corporation plc

*** DIALINDEX search results display in an abbreviated *** *** format unless you enter the SET DETAIL ON command. *** ? set files biochem
>>> 162 is unauthorized
>>>1 of the specified files is not available
You have 22 files in your file list.
(To see banners, use SHOW FILES command)
? s (carbonic()anhydrase) and fsh

Your SELECT statement is:
s (carbonic()anhydrase) and fsh

Items File
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4 5: Biosis Previews(R)_1969-2002/Nov W3
5 34: SciSearch(R) Cited Ref Sci_1990-2002/Dec W1
1 50: CAB Abstracts_1972-2002/Oct
1 71: ELSEVIER BIOBASE_1994-2002/Dec W1
2 73: EMBASE_1974-2002/Nov W4
1 144: Pascal_1973-2002/Dec W1
4 155: MEDLINE(R)_1966-2002/Nov W3

7 files have one or more items; file list includes 22 files.
? rf
Your last SELECT statement was:
S (CARBONIC()ANHYDRASE) AND FSH

Ref Items File
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N1 5 34: SciSearch(R) Cited Ref Sci_1990-2002/Dec W1 N2 4 5: Biosis Previews(R)_1969-2002/Nov W3 N3 4 155: MEDLINE(R)_1966-2002/Nov W3
N4 2 73: EMBASE_1974-2002/Nov W4
N5 1 50: CAB Abstracts_1972-2002/Oct
N6 1 71: ELSEVIER BIOBASE_1994-2002/Dec W1
N7 1 144: Pascal_1973-2002/Dec W1
N8 0 6: NTIS_1964-2002/Dec W1
N9 0 40: Enviroline(R)_1975-2002/Nov
N10 0 65: Inside Conferences_1993-2002/Dec W1 7 files have one or more items; file list includes 22 files.
- Enter P or PAGE for more -
? b n3, n1, n2, n4-7
>>>Ranked file range must be entered as "Nrr - Nrr" (e.g., N1-N10).
>>>"7" is not a valid category or service name
02dec02 13:43:07 User217743 Session D583.4
$0.73 0.419 DialUnits File411
$0.73 Estimated cost File411
$0.21 TELNET
$0.94 Estimated cost this search
$1.25 Estimated total session cost 0.722 DialUnits
SYSTEM:OS - DIALOG OneSearch
File 155:MEDLINE(R) 1966-2002/Nov W3
*File 155: For updating information please see Help News155. Alert feature enhanced with customized scheduling. See HELP ALERT. File 34:SciSearch(R) Cited Ref Sci 1990-2002/Dec W1
(c) 2002 Inst for Sci Info
*File 34: Alert feature enhanced for multiple files, duplicates removal, customized scheduling. See HELP ALERT.
File 5:Biosis Previews(R) 1969-2002/Nov W3
(c) 2002 BIOSIS
*File 5: Alert feature enhanced for multiple files, duplicates removal, customized scheduling. See HELP ALERT.

Set Items Description
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? s (carbonic()anhydrase) and fsh
25227 CARBONIC
21688 ANHYDRASE
21371 CARBONIC(W)ANHYDRASE
57015 FSH
S1 13 (CARBONIC()ANHYDRASE) AND FSH
? rd
...completed examining records
S2 9 RD (unique items)
? t s2/3,ab/all

2/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10499897 20009377 PMID: 10541924
Serum hormone and myocellular protein recovery after intermittent runs at the velocity associated with VO(2max).
Vuorimaa T; Vasankari T; Mattila K; Heinonen O; Hakkinen K; Rusko H Sport Institute of Finland, FIN 19120 Vierumaki, Finland. timo.vuorimaa@vierumaki.fi
European journal of applied physiology and occupational physiology (GERMANY) Nov-Dec 1999, 80 (6) p575-81, ISSN 0301-5548 Journal Code: 0410266
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The responses of serum myocellular proteins and hormones to exercise were studied in ten well-trained middle-distance runners [maximal oxygen consumption (VO(2max)) = 69.4 (5.1) ml x kg(-1) x min(-1)] during 3 recovery days and compared to various measures of physical performance. The purpose was to establish the duration of recovery from typical intermittent middle-distance running exercises. The subjects performed, in random, order two 28-min treadmill running exercises at a velocity associated with VO(2max): 14 bouts of 60-s runs with 60 s of rest between each run (IR(60)) and 7 bouts of 120-s runs with 120 s of rest between each run (IR(120)). Before the exercises (pre- exercise), 2 h after, and 1, 2 and 3 days after the exercises, the same series of measurements were performed, including those for serum levels of the myocellular proteins creatine kinase, myoglobin and *carbonic* *anhydrase* III (S-CK, S-Mb and S-CA III, respectively), serum hormones testosterone, Luteinizing hormone, follicle-stimulating hormone and cortisol (S-testosterone, S-LH, S- *FSH* and S-cortisol, respectively) and various performance parameters: maximal vertical jump height (CMJ) and stride length, heart rate and ratings of perceived exertion during an 8-min run at 15 km x h(-1) (SL(15 km x h(-1)), HR(15 km x h(-1)) and RPE(15 km x h(-1)), respectively). Two hours after the end of both exercise bouts the concentration of each measured serum protein had increased significantly (P < 0.001) compared to the pre-exercise level, but there were no changes in SL(15 km x h(-1)) or CMJ. During the recovery days only S-CK was significantly raised (P < 0.01), concomitant with a decrease in CMJ (P < 0.01) and an increase in RPE(15 km x h(-1)) (P < 0.01). Hormone levels remained unchanged compared to the pre-exercise levels during the recovery days and there were no significant differences between the two exercise bouts in any of the observed post-exercise day-to-day responses. With the exception of S-CK, after IR(120) the post-exercise responses returned to their pre-exercise levels within the 3 days of recovery. The present findings suggest that a single 28-min intermittent middle-distance running exercise does not induce changes in serum hormones of well-trained runners during recovery over 3 days, while changes in S-CK, CMJ and RPE(15 km x h(-1)) indicate that 2-3 days of light training may be needed before the recovery at muscle level is complete.

2/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09794221 98219133 PMID: 9558442
Neither castration nor steroid-replacement change the apparent molecular size of *FSH* in the sheep pituitary.
Kirkpatrick B L; Grotjan H E
Department of Animal Science, University of Nebraska, Lincoln 68583-0908, USA.
Animal reproduction science (NETHERLANDS) Jan 30 1998, 49 (4) p239-46, ISSN 0378-4320 Journal Code: 7807205
Contract/Grant No.: HD18879; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Gonadal steroids alter the apparent molecular size of intrapituitary Follicle-Stimulating Hormone (*FSH*) in rats and monkeys as well as increase the percentage of acidic *FSH* isohormones in sheep. Hence, we hypothesized that the molecular size of ovine (o) *FSH* would be increased by gonadal steroids. Extracts of pituitaries from rams and wethers, as well as, from wethers which had been implanted with dihydrotestosterone (DHT), 17 beta-estradiol (E2) or both steroids (n = 4-6 per treatment group) were subjected to analytical gel permeation chromatography using Sephadex g-100 Superfine. *FSH* concentrations in chromatographic fractions were determined by radioimmunoassays. Although *FSH* in pituitaries of non-implanted wethers eluted slightly earlier (i.e. larger) than *FSH* in pituitaries from E2-implanted wethers as evaluated by distribution coefficients (Kds) during chromatography (P < 0.05), gonadal steroids did not consistently increase Kds but tended to decrease them. When Kds were extrapolated to apparent molecular weights using a series of standard proteins (bovine serum albumin (bSA), ovalbumin (OA), *carbonic* *anhydrase* (CA) and cytochrome c (CC)) that were included in each chromatogram, the differences between treatment groups were not statistically significant (P > 0.05). Thus, in contrast to rats and monkeys, neither castration nor steroid-replacement appears to alter the molecular size of *FSH* in the sheep pituitary as evaluated by analytical gel permeation chromatography.

2/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06261775 89348562 PMID: 2763730
[Effect of allotransplantation of the testis on several metabolism parameters in primary hypogonadism]
Einfluss der Allotransplantation des Hodens auf einige Metabolismus-Parameter bei primarem Hypogonadismus.
Schioschwili T I; Alchasow I W; Saakaschwili T G; Kasabjan E W; Kuraschwili R B; Gaswiani G P; Datikaschwili T S; Ekisaschwili S K Forschungsinstitut fur Urologie und Nephrologie, Ministeriums fur Gesundheitswesen der Georgischen SSR, Tbilissi.
Zeitschrift fur Urologie und Nephrologie (GERMANY, EAST) Jun 1989, 82 (6) p325-30, ISSN 0044-3611 Journal Code: 0413643
Document type: Journal Article ; English Abstract
Languages: GERMAN
Main Citation Owner: NLM
Record type: Completed
The allotransplantation of a testis with immunological control and immunosuppressive treatment may ensure a quite satisfactory hormone compensation and acceptable sexual rehabilitation of patients suffering from primary hypogonadism.

These patients show characteristic biochemical changes: reduction of testosterone, iron and calcium blood concentration and *carbonic* *anhydrase* activity, but increase of *FSH*, LH and oxyproline concentration, whereas content of copper and zinc and activity of transferrine and ceruloplasmin are normal. In cases of successful testicular allotransplantation normalization of the above mentioned biochemical parameters occur together with an improvement of blood hormone balance (increased level of testosterone and decreased *FSH* and LH levels).

2/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

02169630 75213785 PMID: 1151807
Intracellular potentials in cells of the seminiferous tubules of rats. Cuthbert A W; Wong P Y
Journal of physiology (ENGLAND) Jun 1975, 248 (1) p173-91, ISSN 0022-3751 Journal Code: 0266262
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
1. Membrane potentials have been recorded from cells of seminiferous tubules of rats in vitro using micro-electrodes. The value in 808 impalements was -28-2 +/- 0-3 mV (mean +/- S.E.) at 33 degrees C. 2. Increasing the potassium concentration depolarized the cells, a tenfold increase in concentration causing a depolarization of 16 mV. Removal of sodium from the bathing solution caused a hyperpolarization of 3 mV at a potassium concentration of 5-9 m-equiv/l. Removal of chloride and replacement with impermeant anions had no effect on potential. Removal of calcium from the bathing solution caused a minor but significant depolarization. 3. Ouabain (10-3 M), dinitrophenol (2-5 times 10-4 M) or removal of glucose from the bathing fluid all caused depolarization. The membrane potentials of the cells were sensitive to temperature over the range 10-33 degrees C, the apparent activation energy for the reactions maintaining the potential being approximately 6 kcal/mole. 4. Membrane potentials in seminiferous tubules were independent of age of the animal, were insensitive to previous hypophysectomy and were insensitive to a number of hormones (*FSH*, LH, HCG, oxytocin). In high concentration prostaglandin E1 caused depolarization. 5. Acetazoleamide (4 times 10-5 M) caused a rapid, but reversible, depolarization of the tubular cells. This was also true in conditions when the HCO'3/CO2 buffer system was replaced with Tris-buffer. Another *carbonic* *anhydrase* inhibitor (p-sulphonamido-benzoic acid) had similar effects on cell potentials as acetazoleamide. These results are discussed in relation to the nature of the ionic secretion produced in the tubules. 6. Occasional cells showed phasic variations in membrane potential. A possible connexion between these variations and the contractile activity of the tubules is discussed.

2/3,AB/5 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2002 Inst for Sci Info. All rts. reserv.

09196172 Genuine Article#: 377WL Number of References: 28
Title: Biochemical responses of fish exposed to a harmful dinoflagellate Cochlodinium polykrikoides (ABSTRACT AVAILABLE)
Author(s): Kim CS (REPRINT) ; Lee SG; Kim HG
Corporate Source: NATL FISHERIES & DEV INST,HARMFUL ALGAL BLOOMS RES DIV, 408-1 SIRANG RI/PUSAN 619900//SOUTH KOREA/ (REPRINT)
Journal: JOURNAL OF EXPERIMENTAL MARINE BIOLOGY AND ECOLOGY, 2000, V254, N2 (NOV 20), P131-141
ISSN: 0022-0981 Publication date: 20001120
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS Language: English Document Type: ARTICLE
Abstract: To elucidate the ichthyotoxic mechanisms of a harmful dinoflagellate Cochlodinium polykrikoides, biochemical responses of fish exposed to blooms were investigated. Particularly, based on our finding that oxidative damages of gill were associated with fish mortality (J. Plankton Res. 21 (1999) 2105-2115), dysfunction of ion-transporting enzymes and secretion of gill mucus of fish exposed to this bloom species were examined. The susceptibilities of several fishes to C. polykrikoides were different, the active pelagic fishes such as black scraper Thamnaconus sepotentrionalis, red sea bream Pagrus major, beakperch Oplegnathus fasciatus and seaperch Malakichthys wakiyae, were more vulnerable than the benthic fishes, flounder Paralichthys olivaceus and rockfish Sebastes inermis. In addition, the higher the algal cell density, the higher the *fsh* mortality. When the test fishes were exposed to C. polykrikoides of 5000 cells ml(-1), the transport-related enzymes, *carbonic* *anhydrase* and Na+/K+-ATPase activities were significantly decreased. The activity of *carbonic* *anhydrase* was decreased with increasing algal cell density and exposure time. The quantity of total polysaccharide in gill mucus is higher in the fish exposed to C. polykrikoides than in the control fish; the magnitudes were higher in the pelagic fishes than that of benthic fishes. Moreover, a drop of blued pH and oxygen partial pressure (pO(2)) was also observed in red sea bream and flounder subjected to C. polykrikoides. These results suggest that the inactivation of gill transport-related enzymes activities, the fall in blood pO(2) and abnormal secretion of gill mucus by the C. polykrikoides may be one of the principal causes of fish kill. (C) 2000 Elsevier Science B.V. All rights reserved.

2/3,AB/6 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2002 Inst for Sci Info. All rts. reserv.

02306694 Genuine Article#: KR898 Number of References: 21
Title: REPLACEMENT OF THE INVARIANT TYROSINE IN THE CAGY REGION OF THE HUMAN CHORIONIC-GONADOTROPIN BETA SUBUNIT (Abstract Available) Author(s): XIA HY; FERNANDEZ LM; PUETT D
Corporate Source: UNIV MIAMI,SCH MED,REPROD SCI & ENDOCRINOL LABSD5,POB 016960/MIAMI//FL/33101; UNIV MIAMI,SCH MED,REPROD SCI & ENDOCRINOL LABSD5,POB 016960/MIAMI//FL/33101; UNIV MIAMI,SCH MED,DEPT BIOCHEM & MOLEC BIOL/MIAMI//FL/33101
Journal: MOLECULAR AND CELLULAR ENDOCRINOLOGY, 1993, V92, N1 (MAR), PR1-R5 ISSN: 0303-7207
Language: ENGLISH Document Type: NOTE
Abstract: The mammalian glycoprotein hormone beta subunits contain a highly conserved amino acid sequence, Cys-Ala-Gly-Tyr-Cys (residues 34-38 of human chorionic gonadotropin beta), that is denoted as the 'CAGY region'. Using site-directed mutagenesis we have replaced Tyr-37 in hCGbeta, i.e., the invariant Tyr in all known mammalian CG, LH, *FSH*, and

TSH beta subunits, with two hydrophobic amino acid residues, Phe and Leu. The resultant mutant forms were characterized for alpha subunit binding and the resulting heterodimers were analyzed for biological activity using two in vitro assays with transformed murine Leydig cells (MA-10). Chinese hamster ovary cells containing a stably integrated gene for bovine alpha were transiently transfected with a eukaryotic expression vector containing a Rous sarcoma viral promoter and the wild-type and mutant cDNAs. The hCGbeta(Phe-37) mutant bound to alpha essentially to the same extent as hCGbeta wild-type, while the hCGbeta(Leu-37) mutant formed somewhat less heterodimer. The heterologous heterodimeric mutant and wild-type gonadotropins were equipotent in a competitive binding assay with [I-125]hCG. In a steroidogenic assay, the mutant hormones were active, but they appeared slightly less potent than the wild-type form. Thus, this invariant Tyr can be replaced with another aromatic amino acid residue or with a hydrophobic, but not aromatic amino acid residue in hCGbeta without any dramatic effect on function. These results indicate that Tyr-37 in hCGbeta, while not obligatory, may participate, either directly or indirectly, in subunit assembly and that the hydroxyl group may function in a modulatory role in signaling.

2/3,AB/7 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2002 Inst for Sci Info. All rts. reserv.

00705618 Genuine Article#: EN894 Number of References: 0
(NO REFS KEYED)
Title: CHANGES OF METABOLIC PARAMETERS AFTER SURGICAL-CORRECTION OF ABDOMINAL CRYPTORCHIDISM IN ADULT PATIENTS (Abstract Available)
Author(s): SCHIOSCHWILI TI; ALCHASOV IW; SAAKASCHWILI TG; DATIKASCHWILI TS; KURASCHWILI RB; TSANAVA NG
Corporate Source: AP ZULUKIDZE UROL & NEPHROL RES INST,UL ZINANDALSKAJA 9/TBILISSI 380066/GEORGIA/USSR/
Journal: AKTUELLE UROLOGIE, 1990, V21, N6, P320-323
Language: GERMAN Document Type: ARTICLE
Abstract: 22 adult patients suffering from bilateral abdominal cryptorchidism with well expressed secondary sexual vestiges and normal level of testosterone showed cryptic hypogonadism, i.e. increase of *FSH* and LH concentration and decrease of copper level, *carbonic* *anhydrase* activity, hypo- and disporteinemia. In the case of bilateral abdominal cryptochidism ordinary orchidopexy or orthotopic autotransplantation of both testicles decrease the oncologic hazard, improve incretory and excretory function of testicles, normalize *FSH*, LH and copper concentration, *carbonic* *anhydrase* activity and blood protein composition.

2/3,AB/8 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

08910652 BIOSIS NO.: 199396062153
Human recombinant activin-A alters pituitary luteinizing hormone and follicle-stimulating hormone secretion, follicular development, and steroidogenesis, during the menstrual cycle in rhesus monkeys. AUTHOR: Stouffer Richard L(a); Woodruff Teresa K; Dahl Kristine D; Hess David L; Mather Jennie P; Molskness Theodore A
AUTHOR ADDRESS: (a)Oregon Regional Primate Res. Center, 505 N.W. 185th Ave., Beaverton, OR 97006**USA
JOURNAL: Journal of Clinical Endocrinology & Metabolism 77 (1):p241-248 1993
ISSN: 0021-972X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Activin, a stimulator of pituitary *FSH* secretion in nonprimate species, may also act in the ovary to modulate follicular development. To examine whether activin has similar actions in primates, female rhesus monkeys (n = 3/treatment) exhibiting regular menstrual cycles received sc injections of either vehicle or 60 mu-g/kg recombinant human activin-A at 0800 and 1600 h for 1 (acute) or 7 (chronic) days beginning in the early follicular phase. The vehicle-treated monkeys displayed menstrual cycles of normal length, with the follicular (11.3 +- 1.3 days, mean +- SE) and luteal (16.6 +- 1.8 days) phases demarcated by midcycle peaks in serum estradiol (E) and bioactive LH. After the first activin injection, levels of human activin A peaked at 90 ng/mL within 1 h and returned to baseline before the second injection 8 h later. Although serum E and *FSH* levels did not change, LH increased (273%, P lt 0.05) within 8 h. Acute activin treatment increased (P lt 0.05) serum E within 24 h to levels (1290 +- 330 pmol/L) typically observed at midcycle. With chronic treatment, serum E peaked on day 2 (2580 +- 338 pmol/L; P lt 0.05), then declined and rose to a second peak (1680 +- 279 pmol/L) on day 5. During chronic activin treatment, LH levels peaked on day 2 (603 +- 270 ng/mL; P lt 0.05 compared to day 0, 15 +- 7 ng/mL) whereas *FSH* increased progressively until day 5 (937 +- 320 ng/mL; P lt 0.05 compared to day 0, 169 +- 59 ng/mL). After acute or chronic activin, the expected midcycle rises in serum E and gonadotropins were delayed to greater than or equal to day 20 (n = 4) or did not occur before menses (n = 2). Although an enlarged ovary with one greater than or equal to 4-mm follicle was observed by laparoscopy during the late follicular phase in vehicle-treated monkeys, medium-to-large follicles were not visible on ovaries during chronic activin treatment or later at the expected midcycle interval in activin-treated monkeys. Similar hormonal and ovarian events were obtained after activin treatment of amenorrheic monkeys having serum *FSH*, LH, and E levels that were comparable to those at menses in spontaneous menstrual cycles. Thus, exogenous activin stimulates pituitary LH and *FSH* secretion and ovarian estrogen secretion during the early follicular phase in intact monkeys. However, acute or chronic activin treatment did not promote complete follicular development and disrupted subsequent events in the menstrual cycle. The study identifies for the first time potent actions and possible roles for activin in the normal and dysfunctional reproductive cycle in primates.

1993

2/3,AB/9 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

08151557 BIOSIS NO.: 000042120980
COMPARISON OF GENE ORDER OF THREE BOVINE CHROMOSOMAL SEGMENTS TO THE HUMAN AUTHOR: BARENDSE W; ARMITAGE S M; WOMACK J E; HETZEL D J
AUTHOR ADDRESS: CSIRO, TROPICAL ANIM. PRODUCTION,

BOX 5545, ROCKHAMPTON MAIL CENT., QUEENSLAND, AUSTRALIA 4702.
JOURNAL: ELEVENTH INTERNATIONAL WORKSHOP ON HUMAN GENE MAPPING, LONDON, ENGLAND, UK, AUGUST 18-22, 1991. CYTOGENET CELL GENET 58 (1-4). 1991. 2123. 1991
CODEN: CGCGB
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1991
? t s2/kwic/all

2/KWIC/1 (Item 1 from file: 155)
DIALOG(R)File 155:

... 3 days after the exercises, the same series of measurements were performed, including those for serum levels of the myocellular proteins creatine kinase, myoglobin and *carbonic* *anhydrase* III (S-CK, S-Mb and S-CA III, respectively), serum hormones testosterone, Luteinizing hormone, follicle-stimulating hormone and cortisol (S-testosterone, S-LH, S-*FSH* and S-cortisol, respectively) and various performance parameters: maximal vertical jump height (CMJ) and stride length, heart rate and ratings of perceived exertion during an...

2/KWIC/2 (Item 2 from file: 155)
DIALOG(R)File 155:

Neither castration nor steroid-replacement change the apparent molecular size of *FSH* in the sheep pituitary.
Gonadal steroids alter the apparent molecular size of intrapituitary Follicle-Stimulating Hormone (*FSH*) in rats and monkeys as well as increase the percentage of acidic *FSH* isohormones in sheep. Hence, we hypothesized that the molecular size of ovine (o) *FSH* would be increased by gonadal steroids. Extracts of pituitaries from rams and wethers, as well as, from wethers which had been implanted with dihydrotestosterone (DHT), 17 beta-estradiol (E2) or both steroids (n = 4-6 per treatment group) were subjected to analytical gel permeation chromatography using Sephadex g-100 Superfine. *FSH* concentrations in chromatographic fractions were determined by radioimmunoassays. Although *FSH* in pituitaries of non-implanted wethers eluted slightly earlier (i.e. larger) than *FSH* in pituitaries from E2-implanted wethers as evaluated by distribution coefficients (Kds) during chromatography ($P < 0.05$), gonadal steroids did not consistently increase Kds but tended to decrease them. When Kds were extrapolated to apparent molecular weights using a series of standard proteins (bovine serum albumin (bSA), ovalbumin (OA), *carbonic* *anhydrase* (CA) and cytochrome c (CC)) that were included in each chromatogram, the differences between treatment groups were not statistically significant ($P > 0.05$). Thus, in contrast to rats and monkeys, neither castration nor steroid-replacement appears to alter the molecular size of *FSH* in the sheep pituitary as evaluated by analytical gel permeation chromatography.

2/KWIC/3 (Item 3 from file: 155)
DIALOG(R)File 155:

... and acceptable sexual rehabilitation of patients suffering from primary hypogonadism. These patients show characteristic biochemical changes: reduction of testosterone, iron and calcium blood concentration and *carbonic* *anhydrase* activity, but increase of *FSH*, LH and oxyproline concentration, whereas content of copper and zinc and activity of transferrine and ceruloplasmin are normal. In cases of successful testicular allotransplantation normalization of the above mentioned biochemical parameters occur together with an improvement of blood hormone balance (increased level of testosterone and decreased *FSH* and LH levels).

2/KWIC/4 (Item 4 from file: 155)
DIALOG(R)File 155:

...Membrane potentials in seminiferous tubules were independent of age of the animal, were insensitive to previous hypophysectomy and were insensitive to a number of hormones (*FSH*, LH, HCG, oxytocin). In high concentration prostaglandin E1 caused depolarization. 5. Acetazoleamide (4 times 10-5 M) caused a rapid, but reversible, depolarization of the tubular cells. This was also true in conditions when the HCO'3/CO2 buffer system was replaced with Tris-buffer. Another *carbonic* *anhydrase* inhibitor (p-sulphonamido-benzoic acid) had similar effects on cell potentials as acetazoleamide. These results are discussed in relation to the nature of the ionic...

2/KWIC/5 (Item 1 from file: 34)
DIALOG(R)File 34:(c) 2002 Inst for Sci Info. All rts. reserv.
...Abstract: were more vulnerable than the benthic fishes, flounder Paralichthys olivaceus and rockfish Sebastes inermis. In addition, the higher the algal cell density, the higher the *fsh* mortality. When the test fishes were exposed to C. polykrikoides of 5000 cells ml(-1), the transport-related enzymes, *carbonic* *anhydrase* and Na+/K+-ATPase activities were significantly decreased. The activity of *carbonic* *anhydrase* was decreased with increasing algal cell density and exposure time. The quantity of total polysaccharide in gill mucus is higher in the fish exposed to...

2/KWIC/6 (Item 2 from file: 34)
DIALOG(R)File 34:(c) 2002 Inst for Sci Info. All rts. reserv.
...Abstract: the 'CAGY region'. Using site-directed mutagenesis we have replaced Tyr-37 in hCGbeta, i.e., the invariant Tyr in all known mammalian CG, LH, *FSH*, and TSH beta subunits, with two hydrophobic amino acid residues, Phe and Leu. The resultant mutant forms were characterized for alpha subunit binding and the... ...Research Fronts: 001 (GLYCOPROTEIN HORMONE ALPHA-SUBUNIT; HUMAN CHORIONIC-GONADOTROPIN (HCG); OVINE LUTROPIN; HCG RECEPTOR; SYNTHETIC PEPTIDES; RECOMBINANT BACULOVIRUS)
91-4296 001 (PROTEIN FOLDING; HYDROPHOBIC POCKET OF *CARBONIC* *ANHYDRASE*-II; INTERNAL PACKING INTERACTIONS)
91-5983 001 (TRANSCRIBED REGION OF THE HUMAN C-FOS GENE; TISSUE-SPECIFIC ENHANCER ELEMENTS; TRANSCRIPTIONAL REGULATION; EUKARYOTIC CELLS; AP-1...

2/KWIC/7 (Item 3 from file: 34)
DIALOG(R)File 34:(c) 2002 Inst for Sci Info. All rts. reserv.
...Abstract: adult patients suffering from bilateral abdominal cryptorchidism with well expressed secondary sexual vestiges and normal level of testosterone showed cryptic hypogonadism, i.e. increase of *FSH* and LH concentration and decrease of copper level, *carbonic* *anhydrase* activity, hypo- and disporteinemia. In the case of bilateral abdominal cryptochidism ordinary orchidopexy or orthotopic autotransplantation of both testicles decrease the oncologic hazard, improve incretory and excretory function of testicles, normalize *FSH*, LH and copper concentration, *carbonic* *anhydrase* activity and blood protein composition.

2/KWIC/8 (Item 1 from file: 5)
DIALOG(R)File 5:(c) 2002 BIOSIS. All rts. reserv.

ABSTRACT: Activin, a stimulator of pituitary *FSH* secretion in nonprimate species, may also act in the ovary to modulate follicular development. To examine whether activin has similar actions in primates, female rhesus...

...activin A peaked at 90 ng/mL within 1 h and returned to baseline before the second injection 8 h later. Although serum E and *FSH* levels did not change, LH increased (273%, P lt 0.05) within 8 h. Acute activin treatment increased (P lt 0.05) serum E within...

...activin treatment, LH levels peaked on day 2 (603 +- 270 ng/mL; P lt 0.05 compared to day 0, 15 +- 7 ng/mL) whereas *FSH* increased progressively until day 5 (937 +- 320 ng/mL; P lt 0.05 compared to day 0, 169 +- 59 ng/mL). After acute or chronic...

...later at the expected midcycle interval in activin-treated monkeys. Similar hormonal and ovarian events were obtained after activin treatment of amenorrheic monkeys having serum *FSH*, LH, and E levels that were comparable to those at menses in spontaneous menstrual cycles. Thus, exogenous activin stimulates pituitary LH and *FSH* secretion and ovarian estrogen secretion during the early follicular phase in intact monkeys. However, acute or chronic activin treatment did not promote complete follicular development...
...REGISTRY NUMBERS: *FSH*
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...*FSH*
MISCELLANEOUS TERMS: GILL *CARBONIC* *ANHYDRASE*;

2/KWIC/9 (Item 2 from file: 5)
DIALOG(R)File 5:(c) 2002 BIOSIS. All rts. reserv.

DESCRIPTORS: ABSTRACT *CARBONIC* *ANHYDRASE* II CORTICOTROPHIN RELEASING FACTOR V-MYC ONCOGENE ANALOG *FSH* PARATHYROID HORMONE HEMOGLOBIN GENETIC LINKAGE MAP ORDER CATTLE REFERENCE PEDIGREE
? *******logoff
? logoff
02dec02 13:44:23 User217743 Session D583.5
$0.76 0.239 DialUnits File155
$0.20 4 Type(s) in Format 95 (KWIC)
$0.84 4 Type(s) in Format 4 (UDF)
$1.04 8 Types
$1.80 Estimated cost File155
$3.06 0.179 DialUnits File34
$0.84 3 Type(s) in Format 95 (KWIC)
$4.20 1 Type(s) in Format 14 (UDF)
$9.70 2 Type(s) in Format 55 (UDF)
$14.74 6 Types
$17.80 Estimated cost File34
$1.34 0.239 DialUnits File5
$0.32 2 Type(s) in Format 95 (KWIC)
$1.75 1 Type(s) in Format 3 (UDF)
$1.75 1 Type(s) in Format 4 (UDF)
$3.82 4 Types
$5.16 Estimated cost File5
OneSearch, 3 files, 0.657 DialUnits FileOS
$0.43 TELNET
$25.19 Estimated cost this search
$26.44 Estimated total session cost 1.379 DialUnits Logoff: level 02.11.01 D 13:44:24